

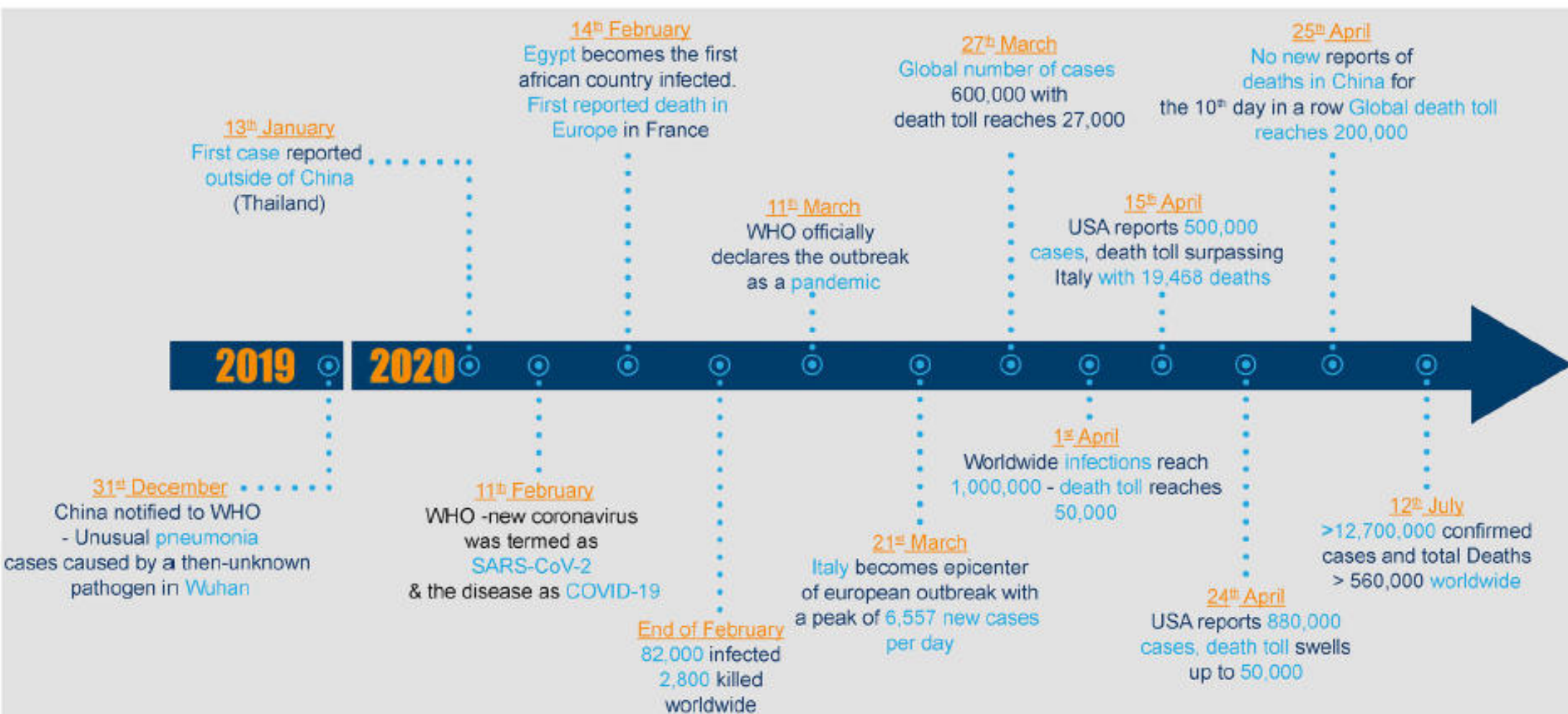
**IMPATTO DELLA INFEZIONE DA COVID-19 SUI FATTORI  
DI VULNERABILITA' LEGATI AL CONSUMO DI ALCOL:  
MECCANISMI DI BASE E PROCESSI DI RECOVERY**



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Dipartimento di Scienze Biomediche  
Università di Cagliari

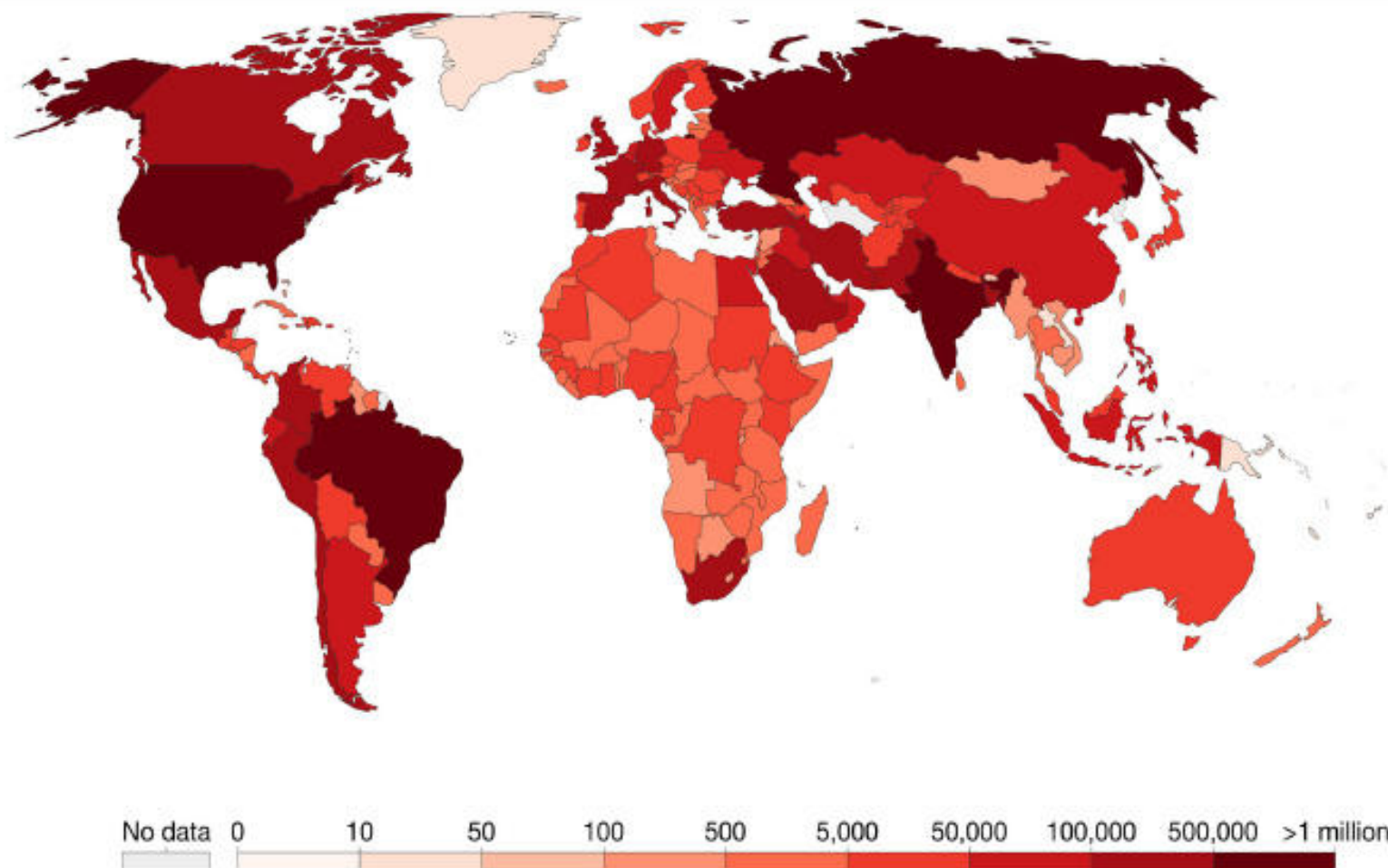
# Timeline della pandemia da COVID-19: eventi significativi



## 12 Luglio 2020: distribuzione globale e incidenza dei casi segnalati di COVID-19 in ciascun paese

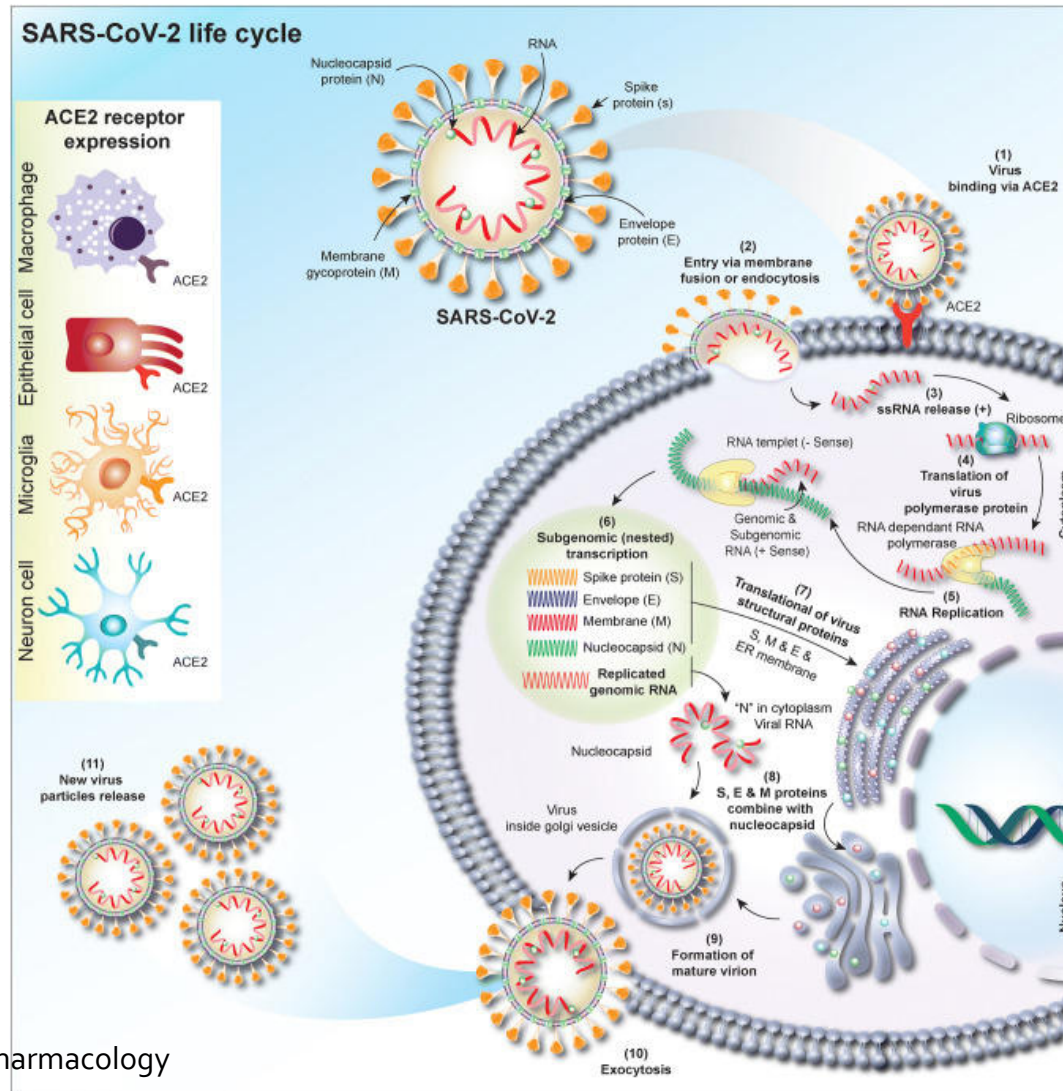
4 27 AGOSTO 2020

Alcol e servizi

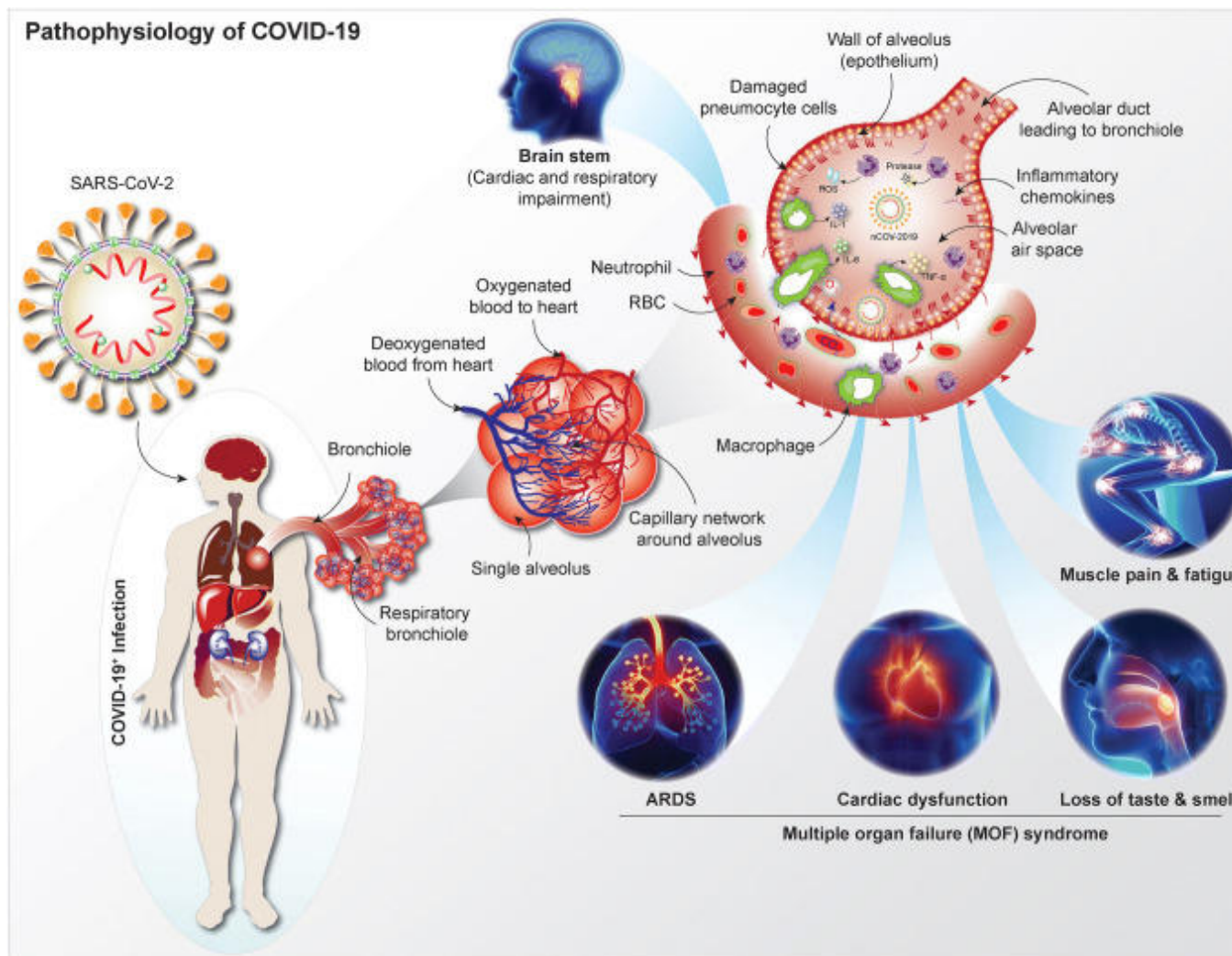


- La pandemia da coronavirus 19 (COVID-19) è causata dal “severe acute-respiratory-syndrome-coronavirus-2” (SARS-CoV-2).
- L’ingresso del virus nella cellula ospite avviene mediante il legame della sub-unità S1 della glicoproteina virale Spike e il dominio extracellulare dell’enzima convertitore dell’angiotensina 2 (ACE-2), nel naso, nel polmone e nella mucosa intestinale.
- Un incremento esponenziale dei casi di COVID-19 è stato osservato in diverse aree a livello globale e il “rate” di infezione del SARS-CoV2 nelle diverse popolazioni è risultato essere legato alle pratiche sociali, alla disponibilità di vaccini e alla diversa frequenza di varianti in geni di suscettibilità.
- La morbilità e la mortalità per COVID-19 è maggiore in persone fragili che presentano co-morbilità.

# Ciclo vitale del virus SARS-CoV-2



# Patofisiologia del COVID-19



## Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic

Jonathan P Rogers\*, Edward Chesney\*, Dominic Oliver, Thomas A Pollak, Philip McGuire, Paolo Fusar-Poli, Michael S Zandi, Glyn Lewis, Anthony S David

### Summary

**Background** Before the COVID-19 pandemic, coronaviruses caused two noteworthy outbreaks: severe acute respiratory syndrome (SARS), starting in 2002, and Middle East respiratory syndrome (MERS), starting in 2012. We aimed to assess the psychiatric and neuropsychiatric presentations of SARS, MERS, and COVID-19.



Lancet Psychiatry 2020;

7: 611-27

Published Online

May 18, 2020

Il confronto con altre infezioni da coronavirus ha mostrato che nei **pazienti affetti da COVID-19** con sintomi lievi sono stati osservati disturbi psichiatrici più gravi tra cui:

- depressione (29%)**
- ansia (34%)**
- disturbo da stress post-traumatico (34%)**

Manifestazioni cliniche dell'infezione da SARS-CoV-2 (COVID-19)

ESORDIO	DECORSO LIEVE	DECORSO GRAVE	SEGNI CLINICI
Umore depresso Ansia Insonnia Irritabilità	Depressione Disturbo da stress post-traumatico	Esacerbazione di patologie neurologiche e psichiatriche (ad es. Alzheimer, <b>Dipendenza</b> ) (Federico, 2020; Singhet al. 2020)	Alterazioni dei livelli sierici di calcio e fosfato (Torales et al.2020)

Review Article

**The outbreak of COVID-19 coronavirus and its impact on global mental health**

Julio Torales<sup>1</sup>, Marcelo O'Higgins<sup>1</sup>,  
 João Mauricio Castaldelli-Maia<sup>2,3</sup> and Antonio Ventriglio<sup>4</sup>



## COVID-19: Quarantine vs. Isolation

**QUARANTINE** keeps someone who was in close contact with someone who has COVID-19 away from others.



**If you had close contact with a person who has COVID-19**



- Stay home until 14 days after your last contact.



- Check your temperature twice a day and watch for symptoms of COVID-19.



- If possible, stay away from people who are at higher-risk for getting very sick from COVID-19.



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**ISOLATION** keeps someone who is sick or tested positive for COVID-19 without symptoms away from others, even in their own home.



**If you are sick and think or know you have COVID-19**



- Stay home until after
  - At least 10 days since symptoms first appeared **and**
  - At least 24 hours with no fever without fever-reducing medication **and**
  - Symptoms have improved



**If you tested positive for COVID-19 but do not have symptoms**



- Stay home until after
  - 10 days have passed since your positive test

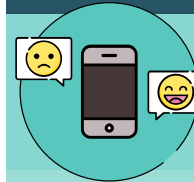


If you live with others, stay in a specific "sick room" or area and away from other people or animals, including pets. Use a separate bathroom, if available.

[cdc.gov/coronavirus](https://www.cdc.gov/coronavirus)



## Coping with stress during the 2019-nCoV outbreak



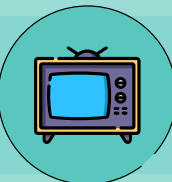
It is normal to feel sad, stressed, confused, scared or angry during a crisis.

Talking to people you trust can help. Contact your friends and family.

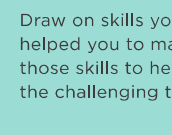


Don't use smoking, alcohol or other drugs to deal with your emotions.

If you feel overwhelmed, talk to a health worker or counsellor. Have a plan, where to go to and how to seek help for physical and mental health needs if required.



Limit worry and agitation by lessening the time you and your family spend watching or listening to media coverage that you perceive as upsetting.



Draw on skills you have used in the past that have helped you to manage previous life's adversities and use those skills to help you manage your emotions during the challenging time of this outbreak.



If you must stay at home, maintain a healthy lifestyle - including proper diet, sleep, exercise and social contacts with loved ones at home and by email and phone with other family and friends.



Get the facts. Gather information that will help you accurately determine your risk so that you can take reasonable precautions. Find a credible source you can trust such as WHO website or, a local or state public health agency.



Neuroscience and Biobehavioral Reviews 106 (2019) 245–262



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

## Neuroscience and Biobehavioral Reviews

journal homepage: [www.elsevier.com/locate/neubiorev](http://www.elsevier.com/locate/neubiorev)



### Review article

## Addiction and stress: An allostatic view

George F. Koob<sup>a,\*</sup>, Jay Schulkin<sup>b</sup>

<sup>a</sup> National Institute on Drug Abuse, United States

<sup>b</sup> Department of Neuroscience, Georgetown University, United States



### ARTICLE INFO

**Keywords:**

Addiction  
 Allostasis  
 Stress  
 Corticotropin-releasing factor  
 Glucocorticoids  
 Extended amygdala

### ABSTRACT

Allostasis, or stability through change, has most often been linked with challenges to homeostasis, in which repeated challenges or stressors produce sufficient allostatic load to generate an allostatic state that can ultimately lead to a disease state. The present review argues that the impact of stress on drug addiction fits with an allostatic model and represents a challenge to brain circuit regulatory mechanisms that underlie the emotional state of the animal. The central thesis is that stress leads to changes in corticotropin-releasing factor in the brain that impact addiction. Stress is further argued to impact all three stages of the addiction cycle—*binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation*—exposing the animal to an emotional allostatic load and allostatic state that forms the growing motivational pathology of addiction. Viewing addiction as an allostatic mechanism provides key insights into the ways in which dysregulated neurocircuitry that is involved in basic motivational systems can transition to pathophysiology.

# Addiction and the Brain Antireward System

George F. Koob<sup>1</sup> and Michel Le Moal<sup>2</sup>

<sup>1</sup>Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla, California 92037; email: gkoob@scripps.edu

<sup>2</sup>Institut François Magendie, Institut National de la Santé et de la Recherche Médicale, Unité 862, Université Victor Segalen Bordeaux 2, Bordeaux 33076, France; email: lemoal@bordeaux.inserm.fr

Annu. Rev. Psychol. 2008 59: 29-53

*Curr Top Behav Neurosci.* 2013 ; 13: 3–30. doi:10.1007/7854\_2011\_129.

## **Theoretical Frameworks and Mechanistic Aspects of Alcohol Addiction: Alcohol Addiction as a Reward Deficit Disorder**

**George F. Koob**

Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 North Torrey Pines Road, SP30-2400, La Jolla, CA 92037, USA

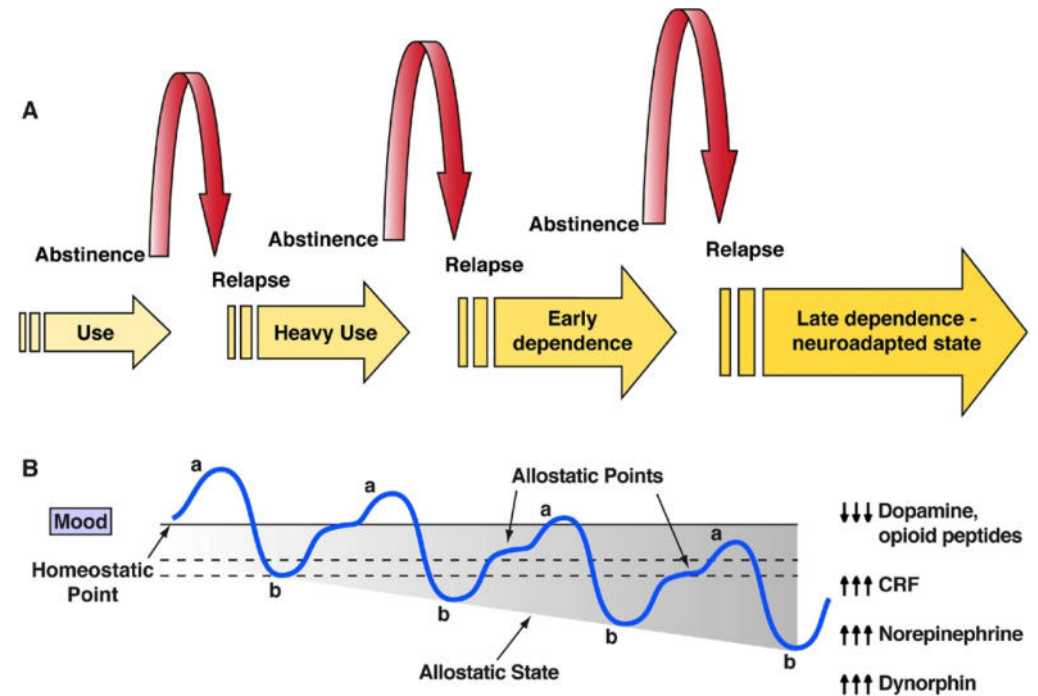
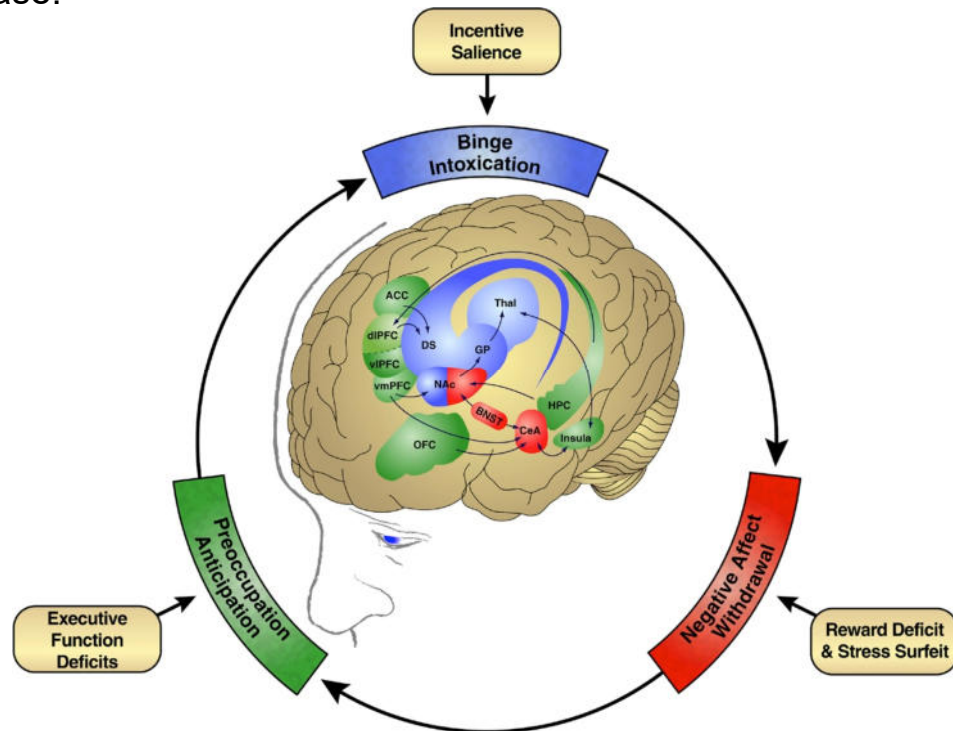
George F. Koob: gkoob@scripps.edu

## Omeostasi

Gli organismi dipendono per la loro sopravvivenza dal mantenimento di certe funzioni entro limiti molto ristretti (omeostasi). Una proprietà intrinseca al concetto stesso di omeostasi è che essa tende a mantenersi in presenza di fattori che la alterano.

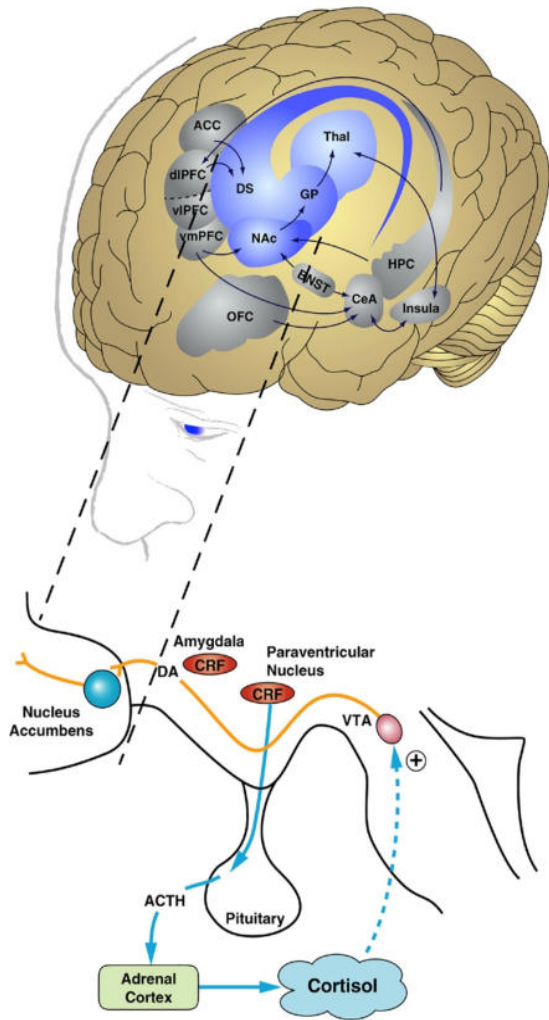
## Processi opposti

In presenza di un fattore che modifica l'omeostasi, l'organismo attiva un processo opposto che produce un effetto di segno opposto a quello del fattore scatenante. Il concetto di processo opposto è stato coniato da Solomon e Corbit (1974) ed applicato alla dipendenza da Koob e Le Moal (1997). Secondo questa teoria, ciascuna dose di etanolo produce l'attivazione di un meccanismo **edonico** che, una volta raggiunto il massimo effetto, si riduce, per tornare eventualmente alla linea di base (a e b). Prima che i valori di base e quindi l'omeostasi venga ripristinata, si instaura un secondo processo, di segno opposto al primo e quindi **antiedonico**, ma più lento rispetto al primo, sia per quanto riguarda l'insorgenza che il ritorno verso la linea di base.



**INTOSSICAZIONE**

**ASTINENZA**

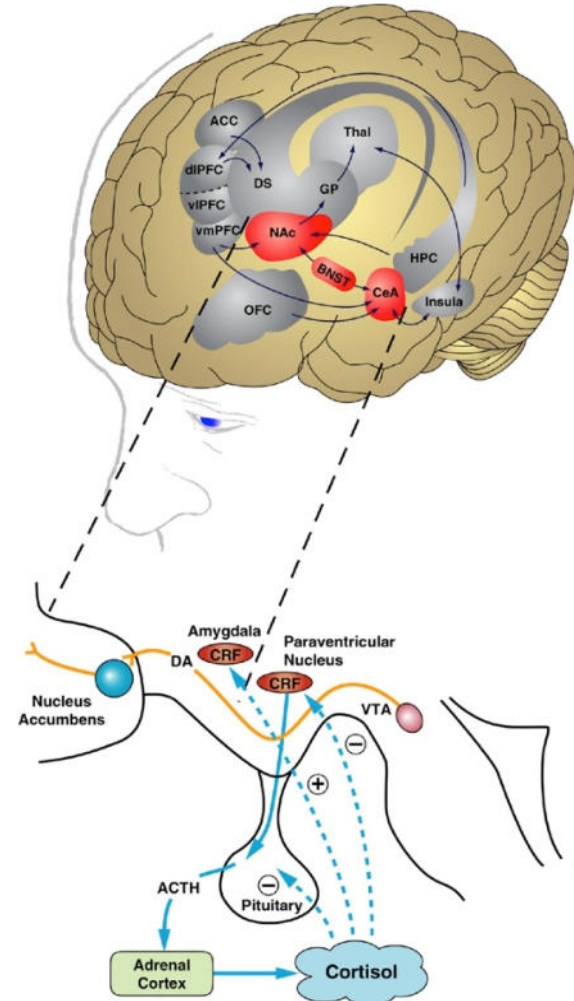


Il **CRF** (fattore rilasciante corticotropina) stimola l'adeno ipofisi a rilasciare l'**ACTH** (ormone adrenocorticotropo) il quale stimola la sintesi dei glucocorticoidi.

Il **cortisolo** facilita l'attività del sistema dopaminergico mesolimbico favorendo il *binge/intoxication stage*

Il **cortisolo** influenza il *withdrawal/inegative affect stage* inibendo il nucleo paraventricolare e stimolando l'amigdala

Koob and Schulkin, 2019



## Substrati neurobiologici per gli effetti acuti di rinforzo dell'alcol

Neurotrasmettitore	Area cerebrale
<b>Dopamina</b>	<i>Nucleo Accumbens</i>
Peptidi oppioidi	<i>Area Ventrale Tegmentale</i>
Acido $\gamma$ -amminobutirrico (GABA)	<i>Amigdala</i>
Endocannabinoidi	

## Neurotrasmettitori implicati negli effetti motivazionali dell'astinenza da alcol

Neurotrasmettitore	Effetto funzionale
↓ <b>Dopamina</b>	<i>Disforia</i>
↓ <b>Serotonina</b>	<i>Disforia</i>
↓ <b>Acido <math>\gamma</math>-amminobutirrico (GABA)</b>	<i>Ansia e attacchi di panico</i>
↓ <b>Neuropeptide Y</b>	<i>Antistress</i>
↑ <b>Dinorfine</b>	<i>Disforia</i>
↑ <b>Ormone di rilascio della corticotropina (CRH o CRF)</b>	<i>Stress</i>
↑ <b>Norepinefrina</b>	<i>Stress</i>

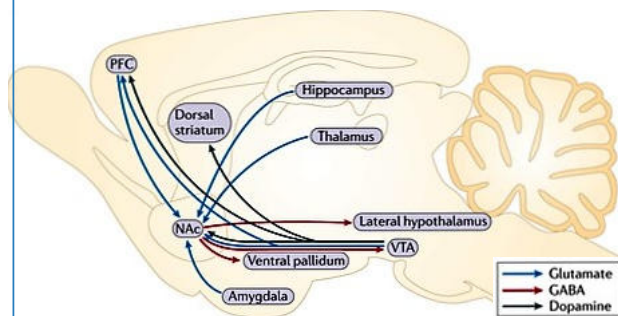
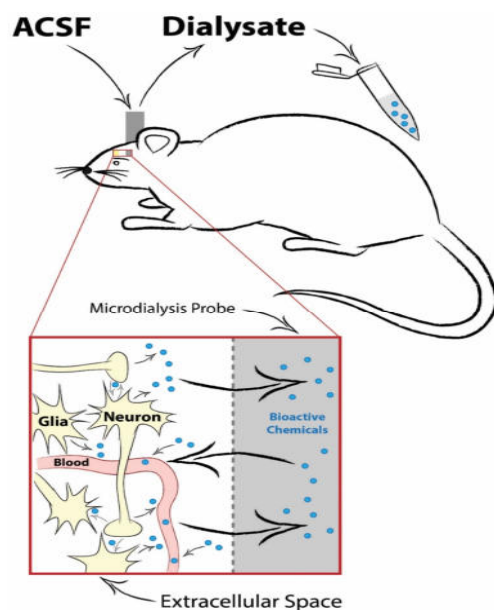
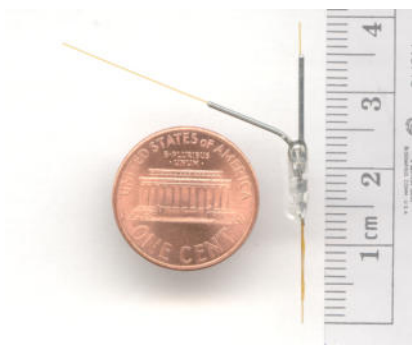
Aumento dei livelli di **dopamina (DA)** extracellulare nella shell del NAc dopo somministrazione acuta di etanolo (10 %, 1 mL, 0.3 g/kg)

Proc. Natl. Acad. Sci. USA  
 Vol. 85, pp. 5274-5278, July 1988  
 Neurobiology

**Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats**

(amphetamine/cocaine/ethanol/nicotine/opiates)

GAETANO DI CHIARA AND ASSUNTA IMPERATO

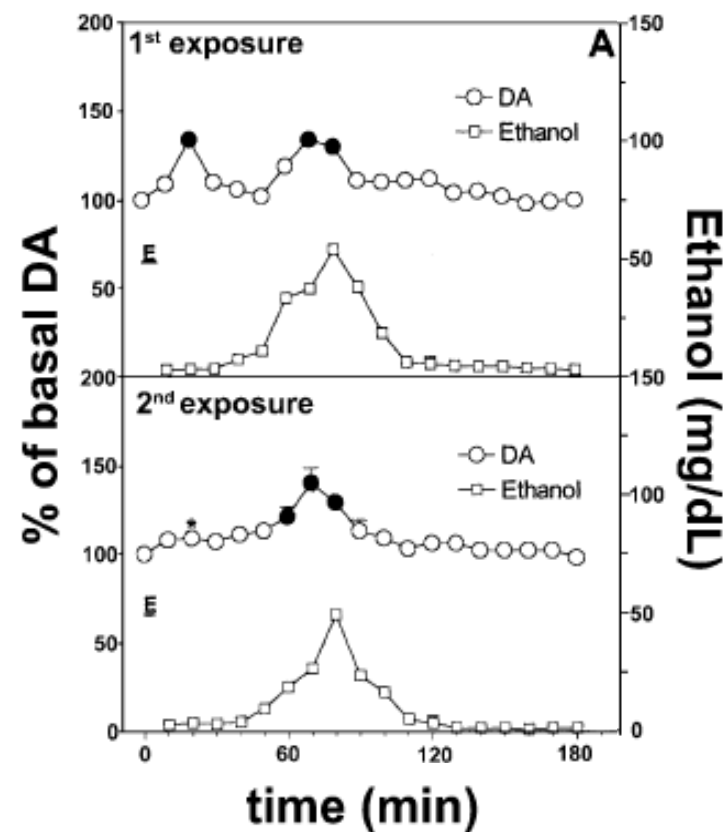


European Journal of Neuroscience, Vol. 17, pp. 1465-1472, 2003

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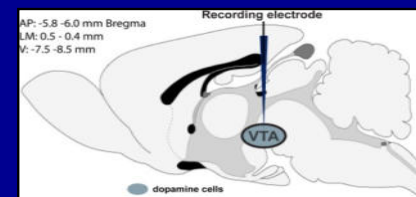
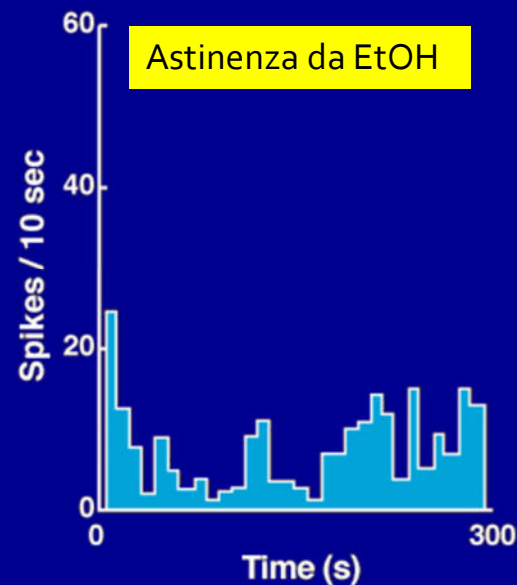
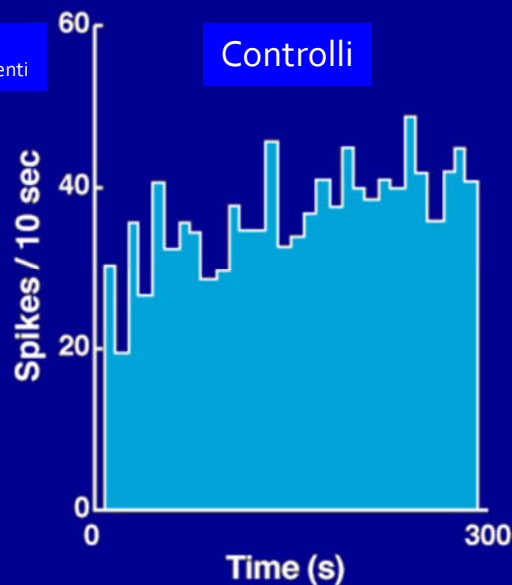
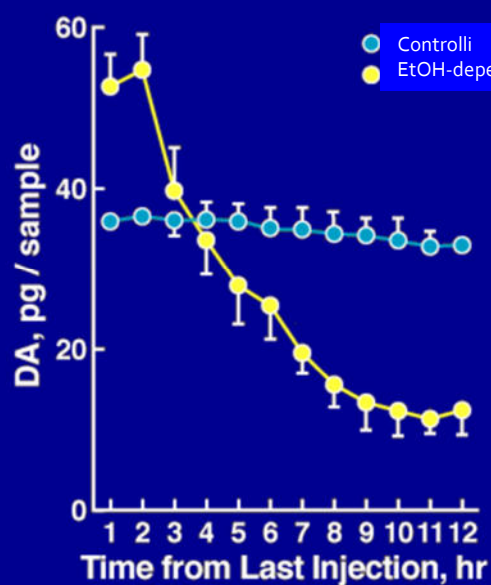
Differential adaptive properties of accumbens shell dopamine responses to ethanol as a drug and as a motivational stimulus

Bassareo, De Luca, ... and Di Chiara



# Ridotta attività del sistema dopaminergico (DA) mesolimbico durante la sindrome di astinenza da etanolo

Somministrazione intragastrica di EtOH per 6 giorni consecutivi  
 Regrazioni elettrofisiologiche da neuroni DA del VTA



From: Diana et al., 1993, Proc Natl Acad Sci USA, 90: 7966-7969.



# Hampered long-term depression and thin spine loss in the nucleus accumbens of ethanol-dependent rats

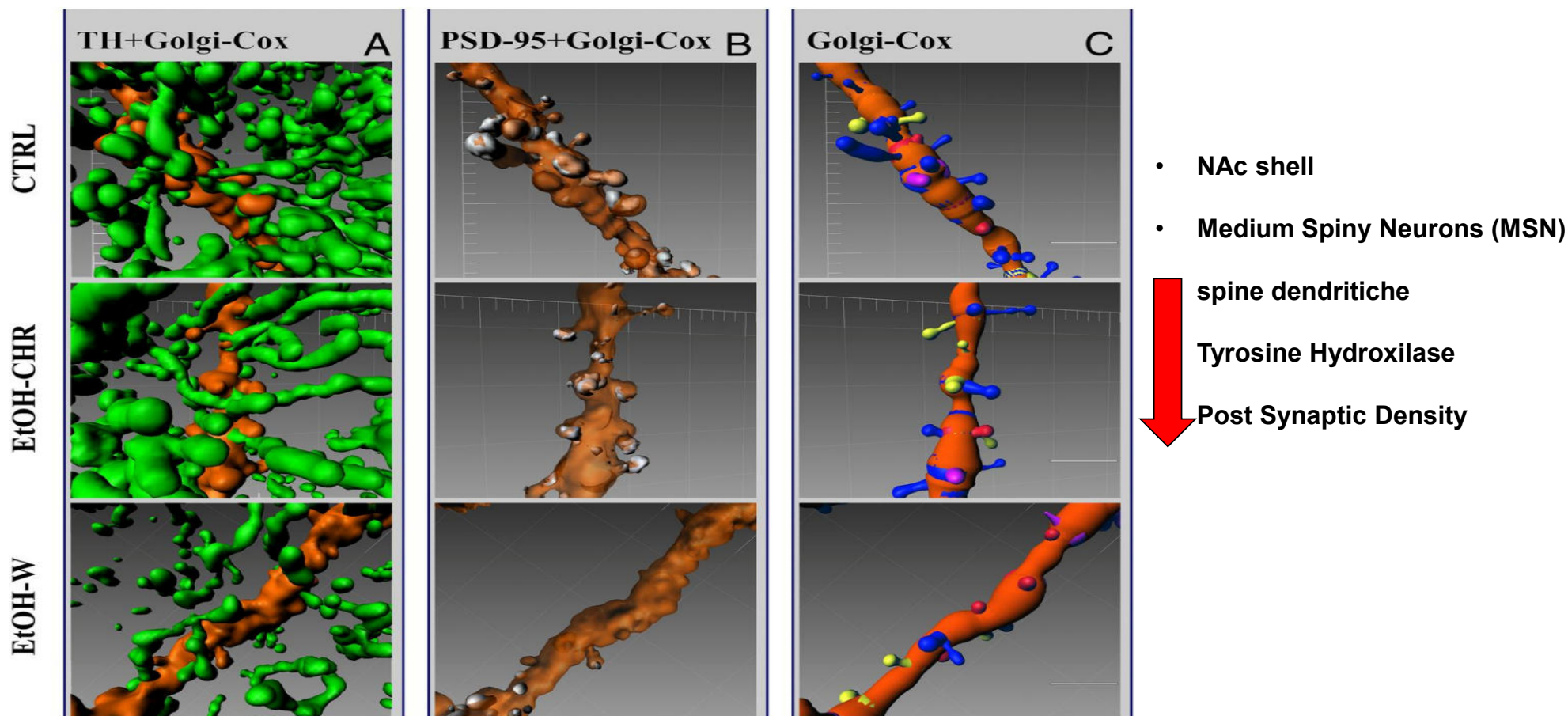
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Alcol e servizi

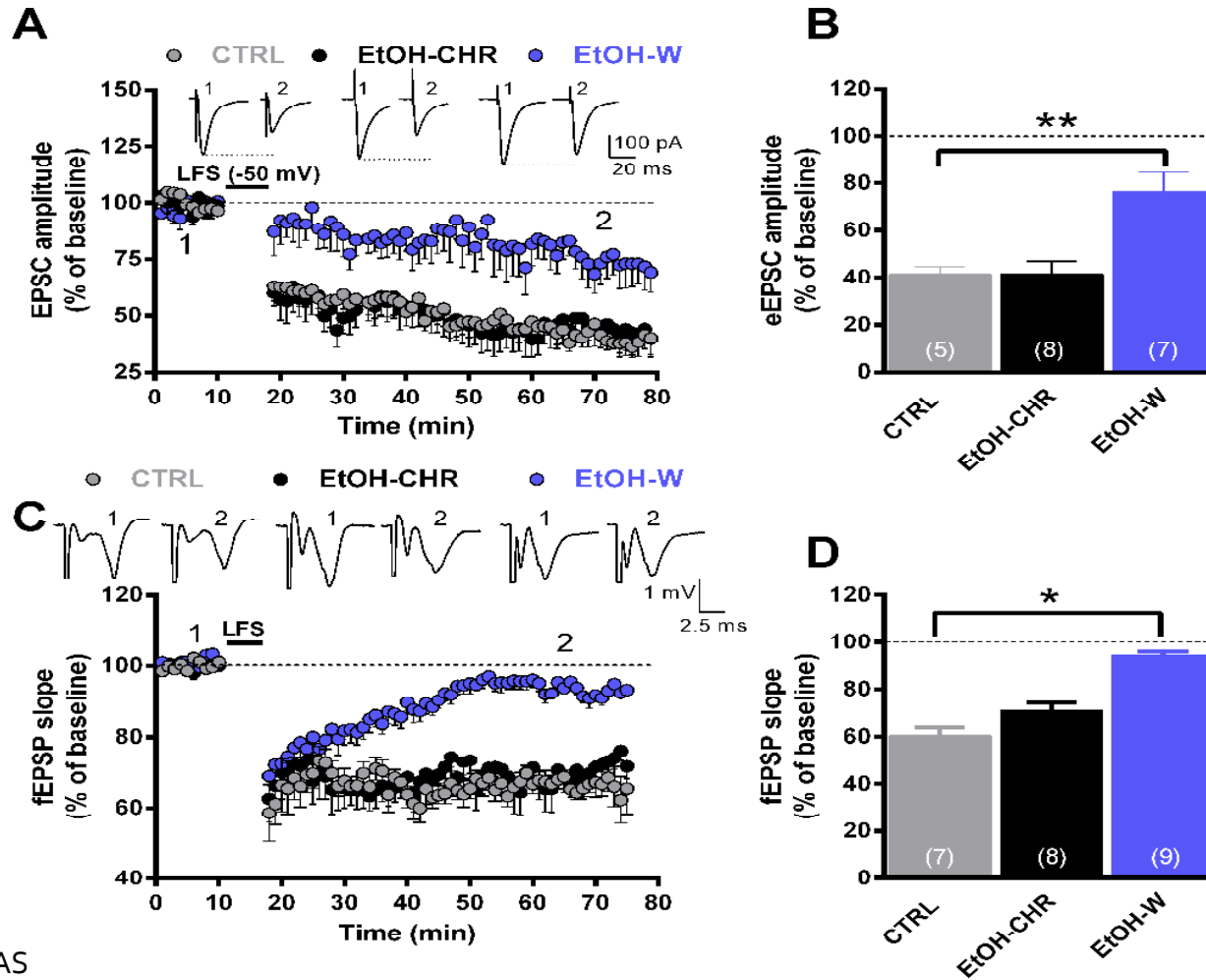
Saturnino Spiga<sup>a,1</sup>, Giuseppe Talani<sup>b,1</sup>, Giovanna Mulas<sup>a,c</sup>, Valentina Licheri<sup>a</sup>, Giulia R. Fois<sup>d</sup>, Giulia Muggironi<sup>d</sup>, Nicola Masala<sup>a</sup>, Carla Cannizzaro<sup>c</sup>, Giovanni Biggio<sup>a,b</sup>, Enrico Sanna<sup>a,b</sup>, and Marco Diana<sup>d,2</sup>

<sup>a</sup>Department of Life and Environmental Sciences, University of Cagliari, 09126 Cagliari, Italy; <sup>b</sup>Institute of Neuroscience, National Research Council, Monserrato, 09042 Cagliari, Italy; <sup>c</sup>Department of Sciences for Health Promotion, University of Palermo, 90127 Palermo, Italy; and <sup>d</sup>"G. Minardi" Laboratory of Cognitive Neuroscience, Department of Chemistry and Pharmacy, University of Sassari, 07100 Sassari, Italy

Edited by Roberto Malinow, University of California, San Diego, La Jolla, CA, and approved July 23, 2014 (received for review April 15, 2014)



# L'astinenza da etanolo (EtOH-W) ostacola la plasticità sinaptica (LTD, long term depression)



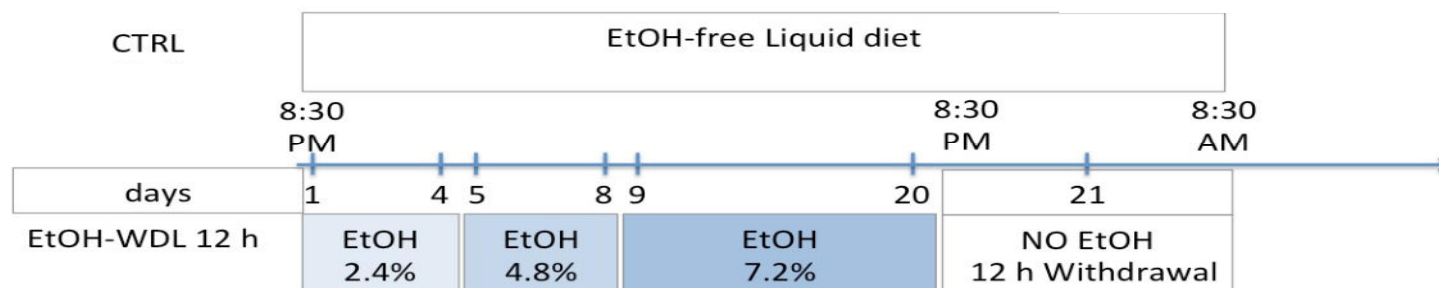
## Dopamine Restores Limbic Memory Loss, Dendritic Spine Structure, and NMDAR-Dependent LTD in the Nucleus Accumbens of Alcohol-Withdrawn Rats

Carla Cannizzaro,<sup>1\*</sup> Giuseppe Talani,<sup>2\*</sup> Anna Brancato,<sup>1</sup> Giovanna Mulas,<sup>3</sup> Saturnino Spiga,<sup>3</sup> Maria Antonietta De Luca,<sup>4</sup> Angela Sanna,<sup>5</sup> Rosa Anna Maria Marino,<sup>6</sup> Giovanni Biggio,<sup>2,3</sup> Enrico Sanna,<sup>2,3</sup> and Marco Diana<sup>7</sup>

### EXPERIMENTAL PROTOCOL

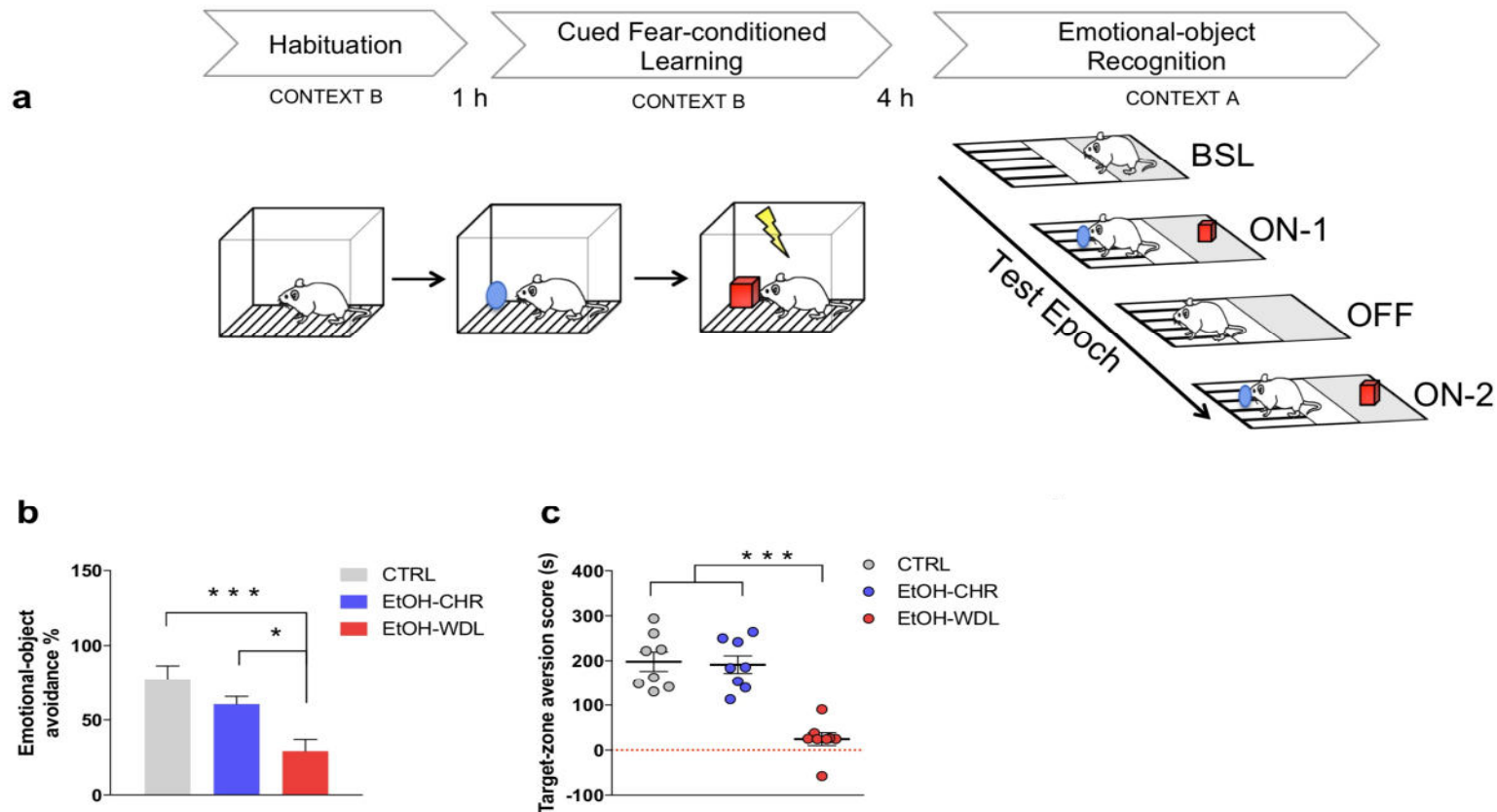
ANIMALS: Male Sprague Dawley rats

DIET: fresh whole cow milk, 910-970 ml, vitamin A 5000 IU/l and sucrose 17 g/l, freshly prepared daily.



From: Cannizzaro et al. *JNeurosci*, 2019, 39(5):929-943.

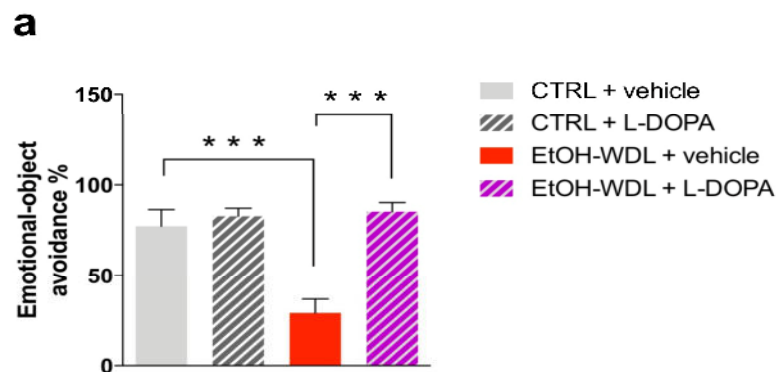
# EOR (Emotional-Object Recognition): l'astinenza da alcol ostacola il processo mnemonico



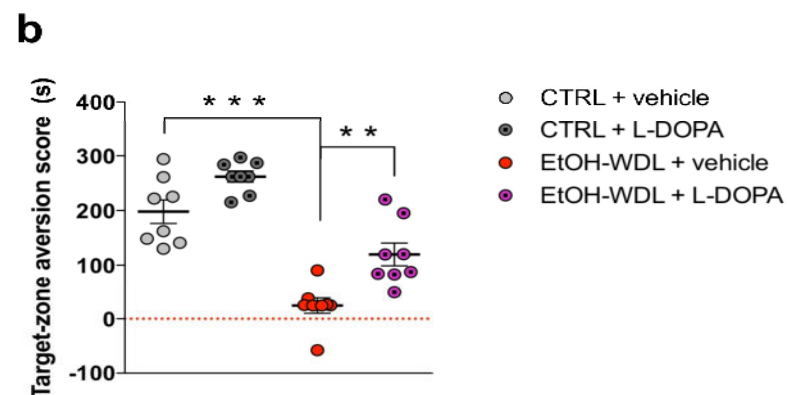
From: Cannizzaro et al. *JNeurosci*, 2019, 39(5):929-943.

EOR task is composed of 3 following sessions: habituation; cued fear-conditioned learning; emotional recognition. Rats are exposed to Context "B chamber" for habituation and cued fear-conditioning, and tested in Context "A chamber" for emotional-object recognition.

Il trattamento con il precursore dopaminergico  
**L-DOPA/Benserazide (6/6 mg/kg sc)**  
 ripristina i processi mnemonici (limbic memories)

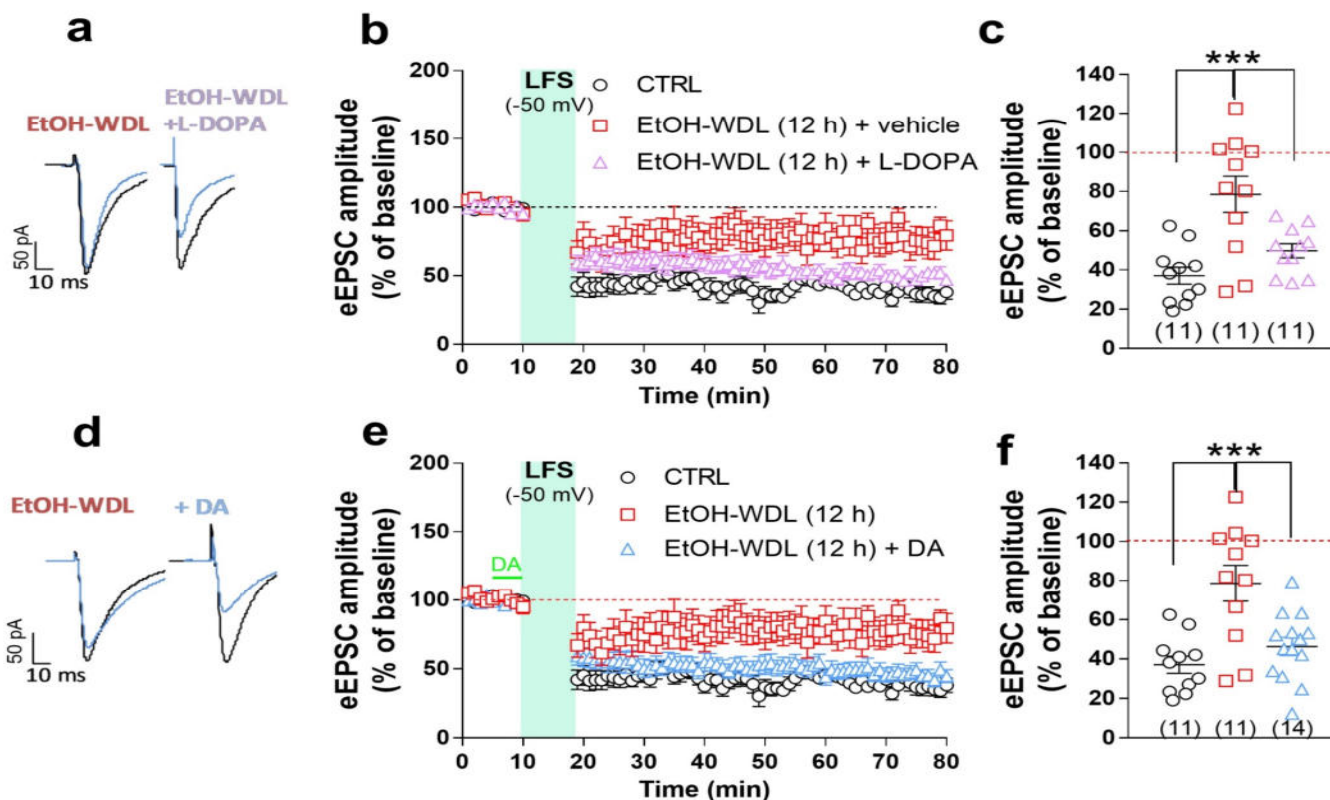


**Emotional Object Avoidance**



**Target-zone aversive score**

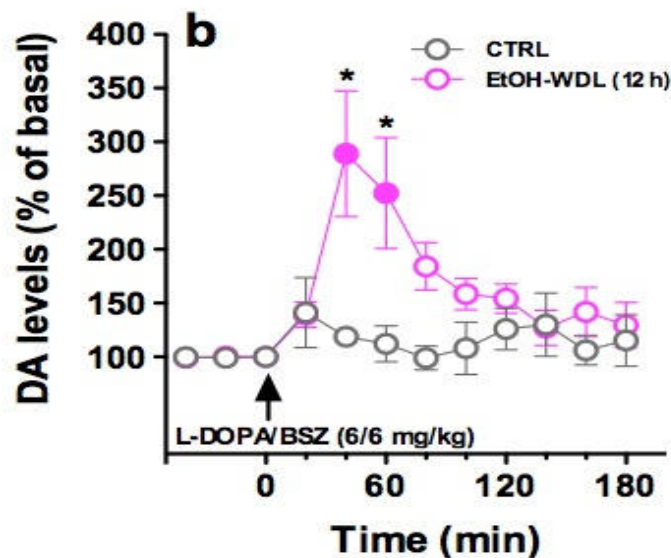
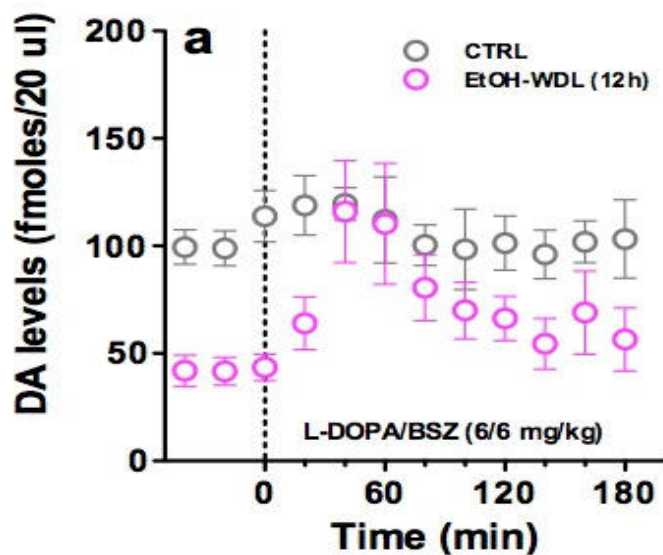
L-DOPA e DA favoriscono la plasticità sinaptica (LTD, long term depression) in preparazioni di MSNs del NAc in animali in astinenza da EtOH



L-DOPA ripristina i livelli di DA extracellulare nel NAc shell di animali in astinenza da etanolo



### NAc shell



### **LA DIPENDENZA DA ALCOL produce:**

- ✓ forme aberranti di memorie emotive, legate ad effetti salienti, questo promuove il consumo crescente di alcol e la ricaduta
- ✓ anomalie sinaptiche strutturali e funzionali in corrispondenza della improvvisa interruzione di consumo di alcol (astinenza)

### **ASTINENZA DA ALCOL:**

- ✓ induce le basi neuroanatomiche e neurofisiologiche sulle quali si sviluppa la disfunzione delle memorie aversive
  - ✓ riduce la trasmissione dopaminergica mesolimbica
  - ✓ altera le connessioni glutamatergiche in the NAc



### LA SOMMINISTRAZIONE DI L-DOPA NELLA ASTINENZA DA ALCOL

- ✓ Aumenta i livelli extracellulari di DA e ripristina la trasmissione DA
- ✓ Ristabilisce la plasticità sinaptica
- ✓ Ripristina la flessibilità dei circuiti neuronali che codificano per informazioni salienti e che sono coinvolti nei processi mnemonici con una salienza emotiva

- 1. Pazienti affetti da forme lievi di COVID-19 possono presentare disturbi psichiatrici (depressione, ansia, disturbo da stress post-traumatico);**
- 1. Stress e isolamento sociale causati dalla pandemia di COVID-19 possono favorire il consumo di alcol e la ricaduta nell'alcolismo attraverso i meccanismi descritti nei modelli animali;**
- 1. Entrambi i fattori dovrebbero essere considerati al fine di informare i consumatori di alcol e il personale dei servizi per le dipendenze che si trova ad affrontare una nuova sfida (diagnosi/terapia da remoto? telemedicina? uso di app e social networks?)**

**Grazie**



**Maria Antonietta De Luca, PhD**

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## EDITORIAL

### Alcohol consumption in the COVID-19 era

Gianni TESTINO <sup>1</sup> \*, Rinaldo PELLICANO <sup>2</sup>

<sup>1</sup>Unit of Addiction and Hepatology, Alcoholological Regional Center, ASL3, San Martino Hospital, Genoa, Italy;

<sup>2</sup>Unit of Gastroenterology, Molinette Hospital, Turin, Italy

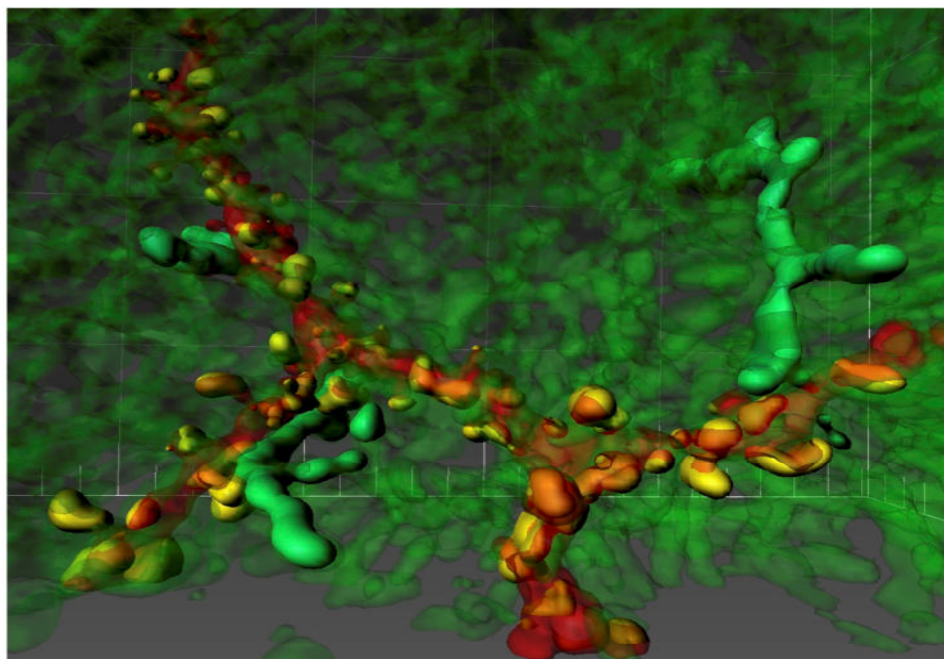
\*Corresponding author: Gianni Testino, Unit of Addiction and Hepatology, Alcoholological Regional Center, ASL3, San Martino Hospital, Padiglione 10, Piazzale R. Benzi 10, 16132 Genoa, Italy. E-mail: [gianni.testino@hsanmartino.it](mailto:gianni.testino@hsanmartino.it)

L'alcolismo cronico riduce l'immunità a virus e infezioni batteriche (Szabo and Saha, 2015; Barr et al., 2016, Chan and Levitsky, 2016).

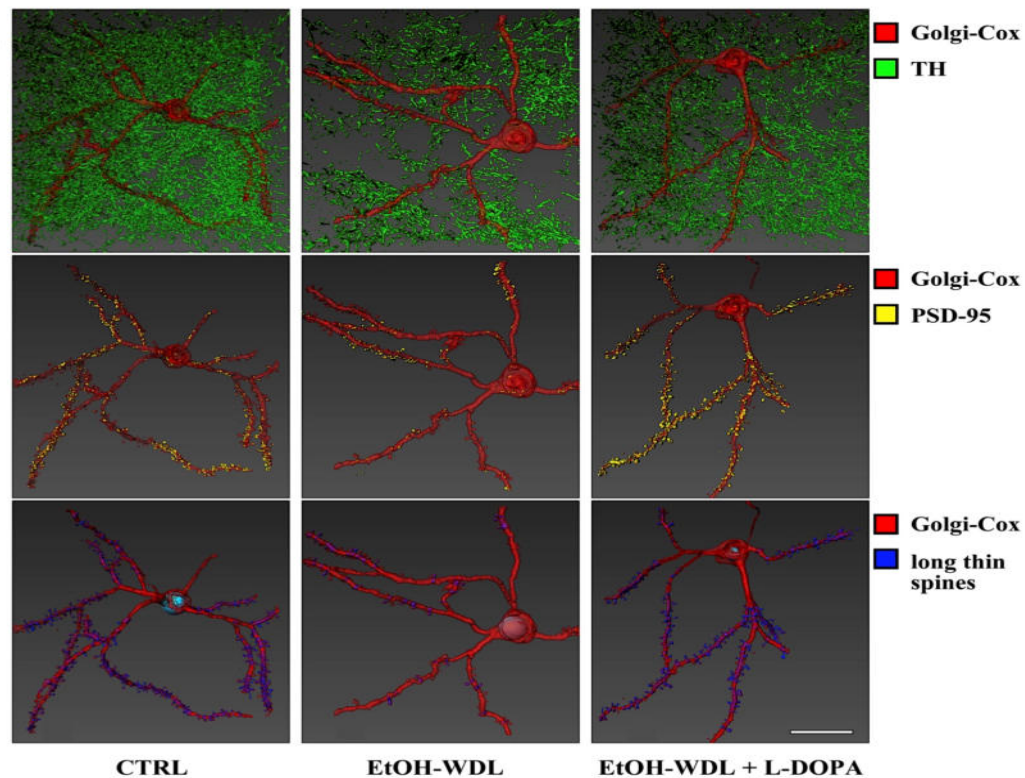
Consumers that exceed the limit of 20-40 g/day of pure alcohol for female and 30-60 g/day for males (1 unit of alcoholics equivalent to the Italian standard of 12 grams of alcohol) are considered harmful drinkers (chronic heavy drinking or CHD). These subjects have an increased risk of infections. In fact, it is well known that a dose-dependent correlation exists between viral infections and alcohol consumption. About 30-40% of patients with alcohol use disorders suffer from hepatitis C virus (HCV). (...) Therefore, in the COVID-19 era, strengthening policies to reduce alcohol intake (no more than one drink/ day) would be likely to reduce the incidence of viral pneumonia. That, especially in older subjects with other comorbidities. In fact, in these subjects, the body can become immune-deficient declining numbers of lymphocytes, resulting in higher susceptibility to bacterial and viral infections

**Figure 3**

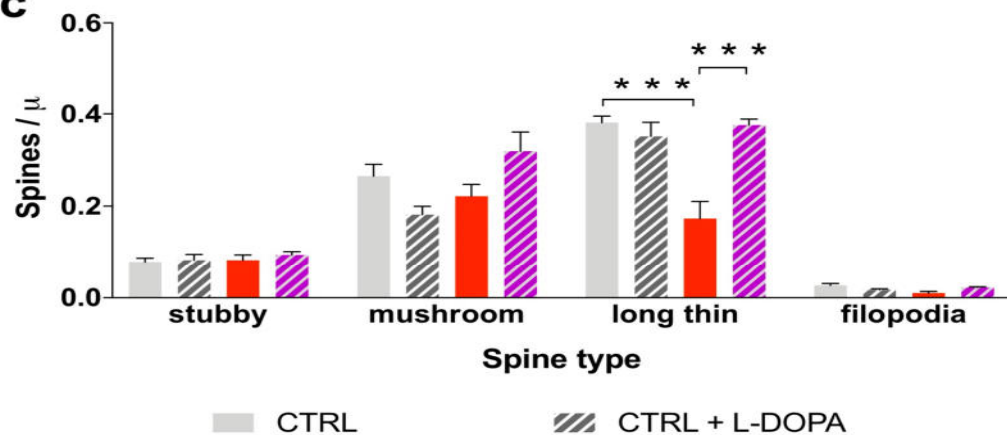
**a**



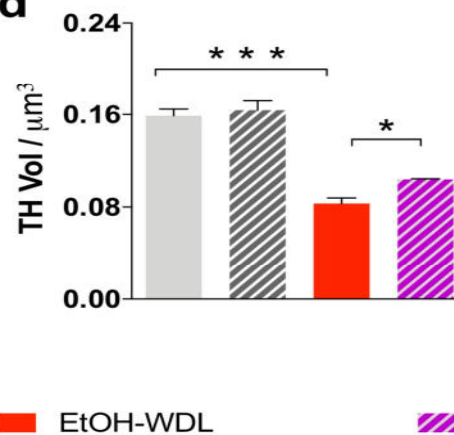
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