

Science AMA Series: Hi Reddit! I'm Olivier George from The Scripps Research Institute, here to answer your questions about how drugs and alcohol affect our neural networks! Ask Me Anything!

Olivier_{George}¹*andr/ScienceAMAs*¹

¹Affiliation not available

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Abstract

Hi Reddit! I'm Olivier George, principal investigator at The Scripps Research Institute and member of the Committee On The Neurobiology Of Addictive Disorders here. My lab recently published a novel study in The Journal of Neuroscience identifying a neuronal network that may be critical for alcoholism. This preclinical study demonstrates that the behaviors associated with alcohol dependence may be reversed by performing a single pharmacogenetic intervention in the brain. The results of this study show that in rats that were heavily dependent on alcohol, both the compulsive alcohol drinking and the physical signs of withdrawal could be reversed back to normal by inactivating a specific neuronal ensemble in a brain region called the central nucleus of the amygdala. A key result in this study is the very long-lasting reversal of alcohol dependence (> 2 weeks) after a single brain manipulation, suggesting that we could use this neuronal network to identify new molecular targets and better medications for the treatment of alcoholism. Our lab is currently working on identifying the brain regions under the control of this neuronal network and on identifying new molecular targets in this network that could be used for medication development. Curious about how addiction works and how alcohol and drugs affect our neural networks? You can also follow our lab on Twitter Read the press release on our research here ** I will be answering your questions at 5pm EST (2pm PST) – Ask Me Anything!**

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OLIVIER_GEORGE [R/SCIENCE](#)

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Read the press release on our research [here](#)

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affect our neural networks! Ask

I am a heavy drinker and have noticed a loss of short term memory. Does giving up drinking repair memory or is the damage permanent? Also how is the "brain manipulation" you speak of achieved?

[bookham](#)

Ok you have to see a physician ASAP. With heavy drinking there is a very high risk of Korsakoff's syndrome associated with loss of memory. This alcohol-related brain neurodegeneration is reversible when the symptoms first occurs if is treated but if left untreated it becomes irreversible and lead to profound amnesia, cognitive impairment and death. Very serious business. Edit: the brain manipulation is actually the use of a compound that inactivate and kills only the neurons that are activated at a specific time (during alcohol withdrawal). you cannot use that in human yet (only animals) as you need to use gene-therapy first to make the neurons sensitive to the compound.

Hi,

Me Anything!, *The Winnower*
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is there any truth in hereditary alcoholism?

Also the older I get, the longer the hangover I endure, what is happening here? (I drink everyday between 3-20 UK units)

Many thanks!

[mr_happy28](#)

Absolutely, Alcoholism has a very strong genetic component. We know some of the genes involved already. We are not all born equal when it comes to alcoholism. there are 2 critical risk factors: 1 if there is a history of alcoholism in your family, 2: age of onset. If you start drinking at ~12 years old you have a 4-5x higher risk to become dependent.

Considering that alcohol use "burns up" the stores of thiamine within the body (liver?) and chronic (and maybe even acute? I don't know for sure) thiamine deficiency can lead to all manner of neurological impairments and condions (Wernicke-Korsakoff syndrome and beriberi are of course strong examples, I'd imagine similar effects can manifest subclinically before progressing to the full blown condition?) in addition to the general impairments caused by both alcohol use and withdrawal - why isn't it more commonly advised that people take vitamin B complex or thiamine supplements prior to drinking to benefit from the neuroprotective effects? Or to go even further - much like bread is regularly fortified with thiamine and other vitamins, would it be possible or advisable to fortify alcoholic beverages with thiamine to reduce their impact on the body's stores? Thanks!

[orbitalfrog](#)

Yes that would be great if it worked, but it doesn't because the defiance in thiamine is only a small part of the neurodegeneration. Yes it can help some patients who have a thiamine deficiency but the majority of chronic alcoholics with neurodegeneration do not. telling people that taking Vitamin B supplement will prevent alcohol-induced neurodegeration is not true and very dangerous.

Does regular use of marijuana have any negative long-term effects on brain function?

[mushroom1](#)

This is a very interesting question, with no clear answers. Study in animals show robust deleterious effect on the brain and cognitive function after chronic exposure. Studies in humans are not so clear. IMO, there is no robust dataset demonstrating that MJ will impair your brain in the long term in ADULT (obviously acutely when you smoke it will make you as impaired as if you were drinking a 6-pack). However, there is some evidence that if you smoke during adolescence then you may produce a long term impact.

How does LSD affect the neural network compared to other substances like alcohol, opiates, etc.?

[Bryanmahindrew](#)

the latest imaging data in humans suggest that LSD affects the brain in a very different way compared to other drugs of abuse. EDIT: see <http://www.ncbi.nlm.nih.gov/pubmed/27071089>

Given the high co-morbidity rate of alcoholism and depression (and other psychiatric disorders), what

impact does inactivating the specific neuronal cluster as mentioned have on psychiatric illness?

Also, after someone becomes sober, are there lingering effects on the brain structure and can those repair themselves naturally? Many psychiatric studies will not admit subjects with a history of alcohol abuse unless the subject is over 6 months sober. Is that because the physical impact of alcohol on the brain (and hormones/neurotransmitters/etc) will screw up the study or is it because the researchers just don't want to have a subject who is recently sober because they think they'll just start drinking again and be an unreliable subject overall? In other words - does six months of sobriety have a significant impact on the physical structures and systems that impact psychiatric illness?

Thank you for doing this AMA and hopefully your research will help many!

[lexiekon](#)

We haven't tested the inactivation on other disorders yet. it would have to be in animal models. You are correct regarding the second part. Yes the reason why these people are excluded are because the lingering effect of a history of alcoholism will bias the study. Yes even after 6 months of sobriety you will most likely still have neuroadaptations and cognitive impairments that are still presents. it takes a long time!

My father used to be a lot more out-going and had a much more keen sense of humor.

He's nearing 60 and he drinks a lot during the free weekends he has. He's had this habit for around 20 years I think. It might be due to old age as well, but I think his tone is a lot "murkier" and he has lost a lot of his ability to joke around stuff. Can the bi-weekend alcohol-binge have an effect on his personality over a long time?

[SendoTarget](#)

yes alcohol has a very powerful effect on mood and it will increase irritability, negative mood and aggressively. It is very clear in human and we see it very well in rodents too.

I quit drinking years ago out of fear that I was becoming an alcoholic. Until recently it required a great deal of willpower to resist the urge to pick the habit back up. Last spring I tried LSD for the first time and found afterwards that I have not had any urges to pick up a bottle since. Is it possible that I stumbled onto a similar mechanism to what you are discussing here?

[TheMightyQuin432](#)

well it is very speculative but it is possible indeed.

With all that you know about drugs and alcohol and its impacts on your brain what are your habits? Do you drink? If so how much? Do you use drugs?

[kysmith1306](#)

Yes i do drink but much less than what i used too. my research calmed me down i guess. I had important issues with drugs and alcohol in the past but i am happy to call it the past.

I have problems with anxiety, and I have noticed that the day after I drink, even if only a small amount, my anxiety is much worse. Why is this, and is there any way to stop it from happening?

[unknown-and-alone](#)

well this is the vicious circle that leads people to fall into alcoholism. Alcohol will improve your mood acutely (most of the time) however, several hours later it will activate your brain stress system without you knowing it. the results is you feel more emotional, anxious, irritable and you often blame someone else (spouse) or something else (work) for your mood and think well let 's have a drink to fix it, and all you do is making it worse.

Have you considered including female subjects in your work? My non-dependent female rats self administer almost twice as much sweetened 10% ethanol as their male counterparts (1g/kg in 30 min vs 0.5g/kg). I'd be really interested in seeing how your ethanol dependence procedure affects this sex difference. And I wouldn't be even a bit surprised if you found sex differences in the role of the CeA in ethanol dependence.

How do you envision your work being adapted for a clinical treatment in the distant future? Do you have the impression that the pharmaceutical industry has interest in your work? Or are these cutting edge techniques simply too impractical for human application in the foreseeable future?

I'm working on neural recording in animals exposed to drugs of abuse and I have a hard time imagining how I could pitch my skills if I were looking for a pharmaceutical job.

[dopameanie](#)

we now always include females to follow NIH's policy but don't have data in this specific study. However, we have data showing like you that females drink more right off the bat ~ twice as much as males. Yes translational outcomes, we won't do pharmacogenetics/optogenetic right now in human, however we can now laser capture these neurons and find a biological marker that is specific of these neurons that can be targeted pharmacologically. This is what we are doing right now, with the hope of finding a new treatment that is specific of these neurons. Experiments in progress... stay tuned!

After a weekend bender, (getting stupid drunk, say, two out of three days), how long does it take your brain to fully recover? I swear I have been "foggy" until Wednesday before.

Note: I don't drink like that anymore. That is a slippery slope

[Hingta](#)

difficult to say it all depends on your metabolism and on how many of these benders you had in the past. in ~12-24h your body will clear the alcohol, but that doesn't end here. there are a lot of neuroadaptation that are happening and that are much slower to reverts. very often we see adaptation that last for 1-2 weeks after such level of alcohol drinking.

By deactivating the area of the Amygdala did you notice any side effects on top of the loss of dependency, be them positive or negative?

[iFr4g](#)

no we haven't noticed any side effects. we measured drinking for water or for a sweet solution in parallel and this manipulation did not affect these behavior. No adverse events (sickness/death) either.

What are your thoughts on the famous "Rat Park Experiment"? How do you view the relationship between addiction and metabolic stress (overactive HPA axis, low oxidative metabolism)?

[nightshade](#)

I have mixed feelings about the Rat Park experiment, only because it was badly interpreted by some to push the idea that drugs are not addictive. Addiction is the results of the interaction between your genes, the drug and the environment. Everybody knows that in the field, we are far beyond the Rat Park experiment. Stress and dysregulation of the HPA axis (not necessarily activation) is a key phenomenon in addiction which contributes to the reinforcing effects of drugs and the maintenance and relapse during abstinence.

This is a pretty amazing study! Congratulations on all your hard work.

I see that disabling the central nucleus of the amygdala does not completely destroy the reward pathway, as the rats still prefer sugar-water. Does this mean rats have a built-in rewards system specific to alcohol? Or might this area of the brain serve as a relay system for certain addiction pathways, rather than being ubiquitous or specific only to alcohol?

[nattywalls](#)

the key here is that it is NOT the reward pathway, it is the stress pathways. we kill the neurons that encodes the "i feel like crap, i want to drink" feeling, not the neurons that encode the "alcohol taste great let's have some" feeling.

I drank heavily from about 15 to 25 years of age. I've been sober for almost 5 years now. What kind of impact would this have had on my development?

[richiecanuck](#)

a serious impact. studies shows that alcohol at that level and that age , interfere with the normal development of the prefrontal cortex which finishes its development on when you reach 21-25 years old. Usually it is associated with a tendency for impulsive behavior and a lower control of your emotions.

Hi there and thanks for doing this AMA!

I have two little questions for you

1. How soon can one expect the results of this research to be applied in the development of a product/medicine, and how long (generally) would that product/medicine take to reach a consumer?
2. This post mentioned it was directly applicable to alcoholism and the related neuronal network, would this also apply to other substance based addictions (opiates, benzos, amphetamines etc)? If not directly, does this research do anything to further the understanding of treating addictions in those respective neuronal networks?

Apologize for the poor wording but I have precisely no education/knowledge in regards to neuroscience.

[Fiftyhourthief](#)

1. this research can't be applied to humans as it is an invasive technique, however now that we

- narrowed down the neuronal network we can go back and see if there are compounds that can specifically target these neurons. We are doing that right now. medication development takes forever because of lack of private and public funding so best estimates would be 20-30 years.
2. Yes, my theory is that this network would be involved in other drugs addiction as well.

Does alcohol have a negative effect on neural networks even when you dont drink huge amounts but consume it regularly (lets say one bottle of beer a day for example), are there any long-term trials on humans for this?

[throwaway235885](#)

there is very little research on the effect of low dose of alcohol (<1 drink/day) on the brain but the NIH is pushing this research, so in a couple years we should have a better idea. My guess is that this 1 drink will have important effects on the neuronal network but that most if not all these effects are reversed in few hours.

Hello Mr George. Thanks for coming by today. My question is simple and timeless. Is there any legitimate ways to avoid or cure a hangover other than abstaining from booze? A part two to that would be, is it common for hangovers to cause a short term state of depression ? I recently dealt with one and I remember feeling despair and anxiety about everything for about half a day. After those feelings passed I just went back to the normal feeling like crap routine for the rest of the day. (Totally not worth it, but it happens sometimes.)

Thanks for all that you do!

[Chromebrew](#)

stay hydrated, and limit your drinking, that's the best way to avoid hangover. regarding the anxiety and depression those are classical symptoms associated with withdrawal from binge-drinking. we see it in human, monkey, rats, mice. The key is to know it and avoid to have that too frequently. the more frequent you have them the more likely you are to become alcoholic.

Which drugs do not harm the frontal lobe and/or pineal gland?

Even though it may be negligible, does one dosage of drugs affect the frontal lobe and/or pineal gland?

I've heard that drugs affect the reward system in the brain. How can this be reversed?

[ChrisTheCoolBean](#)

every drugs of abuse either acutely or chronically affect the frontal lobe. Some drugs will have more of an impact than others and some of these changes are reversible, but others are not, it really depended on the consumption/frequency. Yes drugs hijack the rear system but this is just part of the story. the bigger part to me is that drugs and drug withdrawal hijack the stress and emotional systems in the brain. IMO this is the driving force behind addiction.

Marijuana has a reputation for negatively affecting memory. Has there been research corroborating this, or is this just circumstantial? If this is real, do we understand the mechanism? Is it reversible?

[shaggorama](#)

MJ is producing memory deficits during intoxication and other cognitive impairment: there is no doubt about that. ~12 puffs on a joint is similar to a blood alcohol level >0.08 (DUI). It is also associated with something called the "motivational Syndrome" where the person wants to do lots of things but doesn't do any and it lead to bad grades or bad performance in school. the good news is that quitting reverse these effects, after 2-3 weeks you should be back to normal.

Not sure if this fits here but I'll give it a shot: Why do I feel the effects of alcohol after a few sips of beer? I am not a heavy drinker, perhaps 2-3 drinks a week on average, and I feel dissociated after just a small amount of alcohol. Is it possible my brain/body processes alcohol differently? Do other people report feeling dissociated from themselves while drinking small amounts of alcohol?

[rummel](#)

absolutely! There are huge individual differences not only in the way your body metabolize alcohol faster or slower but also how your brain reacts to alcohol. Some people will feel very tipsy/drunk after very small amount of alcohol, while other will barely feel a buzz. The good thing about being very sensitive to alcohol like you are is that you are in much less likely to become alcoholic because of that. Study show that you are more likely to become alcoholic if you are tolerant to alcohol or if you are tolerant to the withdrawal/hangover.

Hey There,

That bit of brain you found... Is it the same for all addictions, or is it just for alcohol?

Can you "cure" an alcoholic by removing that part, or would that be too damaging? (eg, remove the alcoholic part also removes the keeping-the-heart-beating part).

[Zidanet](#)

there are some ethical issues here in performing brain lesions. some country (china, Russia) have published such brain lesions study in human addicts, but it is very controversial.

Are there any physiological reasons that kappa opioid receptor (KOR) agonists present lower risk for dependence than traditional opiates that act on mu receptors, or is it mostly just a psychological reason, due to appetitiveness?

[thefirebear](#)

yes, absolutely, KOR agonist are aversive, ethyl induce panic attack in humans (similar thing happens in rats). not all the opioids are rewarding. we actually think that KOR activation is in part responsible for the malaise and negative emotional states of drug withdrawal.

How did you define alcoholism? If it 'cures' alcoholism does it also 'cure' social drinkers of wanting alcohol? What about addictions to food? Or exercise? Is it purely a drug/alcohol thing? How amazing.

[redditusername374](#)

we saw no effects on natural reward (sugar/water) and very small effect on binge-drinking, it appears to be specific to alcohol addiction. the way i define it in rats is the moment rats show physical symptoms when you take alcohol away and when they show escalation of alcohol drinking particularly

after abstinence and when they do not stop drinking even if there are negative consequences associated with drinking (aversive event)

Hi, I have a uni essay due on monday that I havnt started yet on drink driving and things done to counter it by the gov. Could you explain why in a few studies people have reported feeling sober enough to drive when in fact they were actually worse of than when they felt too drunk to drive? I can provide/link the study if you wish

[Hellboundbait](#)

Very interesting point. YEs this is absolutely true and there is a name for that. It is called Behavioral Tolerance. You see it in human, monkey, rats, mice. There is a perfect correlation between blood alcohol level and the level of drunkenness at the beginning (30min - 60 min into drinking) but then your brain adapts to the alcohol to maintain your behavior in a normal level (due probably to a desensitization of some receptors activated by alcohol). The consequence is that you feel sober while your blood alcohol level is still very high, as high as when you felt drunk. bottom line, don't trusts yourself and carry a keychain breathalyzer when you go drinking so you don't get a DUI.

I don't know how alcohol dependency works in rats, but in humans it seems to vary wildly: from the half-bottle-of-wine-before-bed-every-night to the liquid lunchers to the person who only drinks - but must drink - in social situations.

Do rats show a variety of dependency models, or are they uniform across the board? Does your research search to 'cure' one form of dependency, or are all forms of dependency essentially the same thing and curable in the same manner?

Thank you.

[Underwaterbob](#)

very good comment, yes there is a lot of individual variability and not all rats become super heavy drinker. In our experimental condition we "on purpose" restrict our study to heavy drinkers to model the most problematic type of dependence on alcohol in human.

What are your thoughts on the famous example of the Vietnam War and the soldiers who easily weaned off Heroin after escaping a negative environment? Do you think social cues play as big a role in drug/alcohol addiction as physiological ones?

[strictlybusiness54](#)

i wouldn't say that they weaned off easily, some of them did, because the environment is critical but it's not the whole story. lots of them stand hooked on heroin. And now we have a HUGE issue with veterans from irk/afganistan developing PTSD syndrome and alcoholism (the former producing the latter)

Hi Olivier, I'm a grad student in the Malinow lab across the street; and TA'd for George Koob before he left for the NIH.

Very cool finding in your JNeuro paper! You might have seen a recent Nature paper by us called [Engineering a Memory](#) where we used optogenetic techniques to stimulate of neural inputs to the

lateral amygdala. Temporally pairing a tone with a shock led to a robust conditioned response in rats; we then replaced this tone with with optogenetic stimulation of neural inputs to the lateral amygdala (originating from auditory nuclei). Temporally pairing the opto neural stimulation CS with a foot shock led to a CR that was sensitive to extinction and blocked by NMDA receptor inhibition during conditioning, indicating the generation of an associative memory. Interestingly we could optically inactivate this memory using 1 Hz LTD stim protocol, and bring it back using a 100 Hz LTP protocol.

I was thinking that it might be interesting to see if the same can be done for alcohol addiction, given that you've already identified the amygdala (CeA) neural ensembles to target.

Also, why do you think the binge-drinking group showed spontaneous recovery of drinking behavior after 24 hours (but not the alcohol dependent group)?

[subroutines](#)

This is very interesting, i will read your paper. YEs the plan is to manipulate this ensemble using ChR/HaloR using a Fos-Cre virus or rat. The last question is what gets me excited about this research. My theory is that in the binge-drinker the neuronal ensemble is not set in stone yet. between days it is not exactly the same set of neurons. in other word if you kill the neurons activated during saturday 's withdrawal then another ensemble will form after the next withdrawal. However, for the dependent rats, the idea is that the neuronal ensemble slowly crystallized so that it is always the same ensemble every time. so this time if you kill it there is no compensations possible.

Hi thanks for doing this. I just want to ask how exactly drugs form dopamine addictions. or if that statement even made sense?

[amarti1021](#)

there is no such thing as dopamine addiction. yes drugs activate dopamine neurons, but being kicked in the balls also probably activates them ;-). the key in addiction is not dopamine or the reward system to me, it is the activation of corticotropin releasing factor and dynorphin in the brain stress system.

Ethically, should we treat alcoholism? We all have to go sometime. So, isn't it better to leave people to their vices?

[Sunfilier](#)

Alcoholism is not a vice, there are decades of brain studies showing that it is brain/mental disorder, yes we should absolutely treat them, it would be unethical not to do so.

Hi Olivier!

I'm a postdoc electrophysiologist at a biomedical research university interested in studying motivation and habitual behaviors. Most of our guidance and training is catered towards applying for junior faculty positions in traditional university settings. With that in mind:

What are the major differences between a faculty position at Scripps or a non-academic research institution and a traditional academic setting?

Are there other experiences or qualifications I should strive for in order to be more competitive for a position at Scripps or a similar non-academic institution?

Bonus science question: Interesting findings! Which circuits downstream of CeA activation do you think

are involved? CeA->BLA->NAc?

Thanks for your time!

[Bro Flacco](#)

Huge differences between Scripps vs traditional academic settings. At research institute like ours it is ALL about RESEARCH, so you need papers with high impact, we spent very little time if any teaching or doing administrative work. In traditional academic institution, PI spend a lot of time teaching and seating in committees and meetings for administrative reasons (university services). If you want to work in the former, focus on research and papers, if you want to work on the latter, make sure you add teaching to your to do list. regarding the circuit, this is a very good question and the answer is that we are not ready to tell (unpublished) but it is not the BLA ;-)

Your research is awesome. Thanks for all your good work.

Can ketamine trigger schizophrenia, or is that bullshit?

[pm me yr succulents](#)

it's a gray area, lot's of drugs and psychedelic drugs in particular can trigger psychotic-like experience or flashbacks of a psychotic experience, however it is unclear if they can produce schizophrenia.

Two questions for you guys:

- 1) Any comment of the neural effects of vivitrol on neural circuitry? Are there any indications of network changes over a long period of time?
- 2) Is there evidence of epigenetic changes for alcoholics? Could this also be a target for therapy?

Thanks!

[DrZack](#)

- 1) i am not very familiar with brain imaging after vivitrol, but i would assume that there would be significant changes in the neuronal networks toward a reversal of the changes induced by opioids.
- 2) yes there are epigenetic changes and several labs in the US are investigating these changes to find new therapies

What is your opinion on diazepam and lorazepam?

[Hitck](#)

very safe drugs as long as you do not drink or take any opiates at the same time.