Science AMA Series: I'm Dr Karen Mifsud, Senior Research Associate at the University of Bristol, I am investigating the processes that occur in the brain after exposure to stress and how these facilitate behavioural responses, AMA!

Karen$_{M}ifsud^{1}andr/ScienceAMAs^{1}$

[1]Affiliation not available

April 17, 2023

Abstract

Hi reddit! My name is Karen Mifsud. I'm Senior Research Associate at the University of Bristol in the Neuro-Epigenetic Research Group. Our current research is investigating how the brain copes with stress. I am specifically interested in the molecular changes that occur in the brain to facilitate adaptive behavioural responses, as a mechanism for coping with stressful situations. This area of research is really important so we can identify impairments in these processes that may mediate the development of stress-related diseases such as Post Traumatic Stress Disorder, Depression and Anxiety. For more information about our research please look here. Given that April is Stress Awareness month I thought it would be a perfect time to take part in an AMA session. I am happy to answer questions on my research, how animals are used in science, careers in science etc. so 'Ask me Anything!' I'll be back to asnwer your questions at 10am ET/3pm GMT. AMA! This AMA has been organised by Understanding Animal Research and The Physiological Society. Edit 2: Thank you for all the questions and I'm sorry I did not get round to answering you all. Many of you have asked how you can cope better with stressful situations, well, after this hour long increase in my stress levels I will be attacking my easter egg stash to facilitate an appropriate recovery ?

the WINNOWER

REDDIT

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KAREN_MIFSUD R/SCIENCE

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Is it possible to reverse any damage that has been done because of stress such as learning or focusing abilities?

Does growing up in a stressful environment forever change the way a person processes emotions and approaches life situations?

GonnaEatYourIcecream

See response to EtuBrut – essentially yes it is possible to reverse these effects, although due to difficulties studying the epigenome in human brains the strongest evidence for this comes from rodent models. I understand that some intervention programmes are occurring in the UK whereby young mums with a history of early life stress are receiving extra support thoughout their own pregnancies/postnatal period to try and break a common cycle of stress being passed down the maternal line most likely via epigenetic. I have not heard the outcome of these interventions as I think it is too early to tell but changing the epigenome does seem possible.

This does not mean that all people or rats exposed to *in utero* or early life stress are going to pass

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these epigenetic changes on as many remain resilient - it will be great to understand why some individuals pass on these changes and others don't but only time will tell.

Humans have developed a natural fight or flight mechanism to stressful situations; however, work, family, and social constructs have created a stigma that these instinctive responses are inappropriate. How do we reconcile this difference and better yet, should we? Where do we draw the line?

ironw00d

I agree with /u/yea_tht_dnt_go_there - there is definitely a freeze aspect to the natural stress response which is very important to accurately appraise the situation. Whilst our behaviours within these categories of fight, flight and freeze may have changed I still feel the instincts remain. For example we still challenging unacceptable behaviour and remove ourselves from stressful situation. There is also a period after exposure to a stressor when we take time to assess the situation in order to make the best choice of response for our protection (do we get involved or not?). In our experiments with rodents we see examples of all of these natural behaviours upon exposure to stressors. Furthermore these different behaviours from different rats in response to identical stressors indicate a very personalised response even in our inbred strain.

Are the stress related changes to the epigenome permanent, or can they be reversed - perhaps through future medication?

I'm going through my A Level right now and my stress levels are orbital.

etubrut

Epigenomic changes in the brain can be long lasting but are not always permanent. Some drugs have been shown to reverse early life stress-induced epigenomic changes in rodents. Over the last few days at #BNA2017 and at the 1st Munich Winter Conference on Stress there have been some great talks on this topic. You do have to remember that not all stress is bad and it can be beneficial to performance so you shouldn't worry about feeling stressed for specific period. If, however, you start to not ever feel relaxed then you may want to get some advice on how to reduce your stress levels and there are some great charities like MIND and MQ which can be approached for this type of advice.

Could you say something on meditation and which kind of meditation is most helpful? Also I'm interested if you personally think that getting rid of ego would help much faster than classic therapy that focuses on dealing with the self. Thank you for doing the AMA!

kodysatdown

This is a growing area of scientific interest. I don't have experience of this line of evidence myself but a small to moderate effect of mindfulness meditation on some of the symptoms associated with high stress such as anxiety/depression Goyal et al 2014.

Hi Dr. Mifsud, thanks for doing this AMA.

If you could do any basic research, (without the need to justify to a grant committee) what would you do? Put another way, are there any questions in this area of neuroscience that you would love to have answered, but don't necessarily think will have money thrown at them to get answered anytime soon?

Also, I've always been extremely interested in both glia and the brain ECM. Is anyone in your group looking at changes in the molecular changes in these (often overlooked In my opinion) parts of the brain?

Has the use of CRISPR or other newer investigative techniques influenced the direction of research in your lab? If so how?

Thanks again!

SarcasticGiraffe

I have to agree with you and if I could choose an area to investigate with unlimited funds I would look at the role of the ECM in the stress response as, like you, I feel this is a really understudied, important area. The hippocampus is the part of the brain required for the formation of stress-related memories. These memories facilitate the formation of adaptive responses (improved coping behaviours upon re-exposure to the stress) and required integration of new neurons into the brain circuitry. To do this the new neurons need reorganisation of the extracellular matrix but as you say these processes have been poorly studies to date. Maybe if you ask me in 10 years time I may be able to shed light on this issue.

As we, in the Neuro-Epigenetics Research Group led by Prof. Hans Reul, are interested in how stress is modulated in the brain we are planning on developing both CRISPR/Cas9 and chromatin confiramation capture (3C) methods to try and get a better understanding of the function of these receptors in stress responses.

If stress can 'turn on' certain genes do you feel that this is why mental illness has become more prevalent in our society? How can we combat this? I'm talking specifically about bipolar disorder.

crzyqltr

Stress both turns on and turns off a variety of genes by probably a wide variety of mechanisms but the links to prevalence of mental health disorders which are indeed more prevalent (although some may argue part of this prevalence is increased awareness of these disorders) are still for the large part unclear. To tackle this increasing trend of mental health disorders I think there should be better investment in mental health research since funding accounts for only ~5% of UK budget but mental disease makes up almost 25% of UK disease burden. There also needs to be a focus on early intervention as these seems to have the best outcomes for preventing lifelong illness.

Hi there! Do you have any insight on the long-term effects of stress experienced during early childhood?

arumi_kai

See earlier responses to /u/GonnaEatYourIcecream and /u/EtuBrut. This is a fascinating field of research but I don't directly study this.

A certain amount of stress is a good thing, right? It's basic biology... but as I understand what you are looking at, chronic stress can cause changes in brain chemistry. What's the most damaging thing about chronic stress?

Thanks for doing this AMA...

FYI I'm unstressed in ☺

seriouslyultrame

There is an inverse 'u' shaped relationship between stress response (CORT hormone) and performance, so you are indeed right it is believed there is a 'good' amount of stress. Our research investigate molecular processes occurring in the brain after acute stress not chronic stress although we are in the process of developing a model to investigate how stress-induced molecular changes differ between acute and chronic conditions.

Hello have you noticed a significant difference in brain response when the cellular metabolism is primarily fueled by beta hydroxy butalate versus glucose?

In other words does a stressed person function differently if recieving BHB whether its endogenous or exogenous.

EDIT: I've seen tons of anecdotal evidence to suggest long term fasting can cure or relieve ptsd but no actual study or evidence to support (or disprove) it.

J_T_Davis

We haven't looked into this but something to try in the future.

When studying animals for psychological research, do they show similar ranges of stress-coping etc. that humans do? For example, something that shocks someone could be much less bothersome to someone else.

As a follow up, do they express these differences in similar ways e.g. eating more, becoming insular or agitated?

Genuinely curious as to whether this is unique to people or not.

MrWendelll

We see a range of stress coping behaviours in our rodents, for example when exposed to the fear conditioning paradigm some rats freeze, some become aggressive and some just run around so even in our inbred strain there appears to be individual differences.

Hey Dr., thanks for the AMA! Two questions:

How do you quantify stress/responses to stress and how are these standardized across experiments?

How do you do "stressless" controls? Wouldn't the absence of stimuli be "stress-inducing," to an extent?

Being a student in biochem where a lot of the stuff I learn is experimented on in vitro and confirmed in vivo (pretty straightforward), neurosci/psych sounds more ambiguous and is honestly pretty foreign to me. Sorry if my questions are nonsense.

bloodyurine

To determine the Hypothalamic-Pituiatry-Adrenal response to the stressor we can measure the level of stress hormone directly in the blood of individual animals. We use a technique called chromatin immunoprecipitation (ChIP) to measure how much receptor is binding to the DNA and Quantitative Polymerase Change Reaction (qPCR) to determine how gene expression is changing in response to

stress.

Baseline animals are killed immediately from their home cage and have very low levels of circulating stress hormone. We do subject these rats to the same handling procedure as the 'stressed' rats and they are also used to having cages picked up etc.

R U focussing on the HHPA axis or more down stream functions to attenuate cortisol and other neurotransmitters?

howtodoit420

We do indeed focus our attention on the hippocampus and also measure CORT responses from HPA activation. We are specifically interested in how the receptors in the brain which respond to the hormones affect gene transcription. Our recent work identified additional levels of regulatory control acting on this system at the level of the hippocampus.