European College of Neuropsychopharmacology – press release

Gene which decreases risk of social network-related stress, increases finance-related stress risk

Type of study: not peer-reviewed/observational/people

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Researchers have discovered that the same gene which increases your risk of depression following financial stress as you grow older also reduces your chance of depression associated with friendship and relationships stresses when young– your social network.

This may have implications for treatment, but also offers a possible answer to a question which has puzzled scientists: why has depression survived through evolution? This work is presented at the ECNP Congress in Barcelona.

5-HTTLPR, which is found on chromosome 17, is a form (a *variant*) of the gene which carries the instructions for producing the serotonin transporter protein, which is central to the pharmacology of depression: antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs, e.g. Prozac, Paxil, Zoloft, and others) are the mainstay of drug treatment for depression. One of the two variants of 5-HTTLPR, the short (s) variant is generally thought to promote a tendency to depression, although as depression is associated with many genes, there is no single genetic cause of depression.

For an inherited trait to survive over time, there normally needs to be some advantage to it being passed on, but with depression there is no obvious reason why evolution should allow a tendency to depression to survive.

Now scientists have found that the s variant (5-HTTLPRs) of this gene may help protect against the depression associated with stressors and life events deriving from the social network in younger people. In previous work, the same scientists had found that the 5-HTTLPRs variant does not increase the depression risk following exposure to most types of stressors as had been believed, but in fact may actually only increases the risk of depression following financial stress in older males.

Researcher Dr Xenia Gonda said: "What we see is the same gene having opposite effects following different types of environmental events and even at different points throughout one's life. For people under around the age of 30, their social network of friends and acquaintances is vitally important. This is the period when they are looking to form attachments. In this younger age, we found that the 5-HTTLPR s variant protects people against depression when exposed to social network stress. However, our previous work showed us that the same gene variant tends to make people more susceptible to depression if they experience financial stress when they get older.

With the older group, we found that if we looked at the two genders separately, this effect was observable only in men, whose traditional gender role is that of the provider for the family so that's perhaps why financial problems may be more stressful for them".

For the latest work, the team had enrolled a sample of 1081 volunteers from Budapest and Manchester, all under the age of 30, and questioned them about 4 different types of stress experience including relationship problems, illness or injury, financial difficulties, and stresses related to the social network such as friends and acquaintances. They found that the short variant of 5-HTTLPR, which is present in around 37-40% of the Caucasian population, conferred a statistically significant protection against depression risk following social network problems, but not against the other stressors in the study.

Dr Gonda continued, *"Depression is not a single disease, and depression related to different types of genes and different stresses may respond to different types of pharmacological and psychotherapeutic treatment. What our study shows that genes involved in depression may actually have positive effects which can also be exploited for therapy. For example those with higher social sensitivity conferred by the s allele may respond better to psychotherapy than those who do not carry this variant, however, further studies would be needed to confirm this.*

It's a subtle distinction, but we believe depending on the environmental context, 5-HTTLPR may have both negative and positive effects; so sometimes it may promote depression, but in certain circumstances, like when exposed to life events and stressors affecting the social network, it protects. We should always consider the possible ancestral context when looking at the adaptive or risk side of genes, and it appears that the adaptive role of 5-HTTLPR was to increase sensitivity to social influences and events with positive outcomes, and its negative effect like increasing depression risk appear only in case of a few types of stress. And this is probably why these genes have been preserved in evolution. But we need to remember that there are multiple genes involved in depression which interact with one another and with the environment, so it's not as simple as saying 'this gene causes depression'.

The take-home message from this work is that "depressogenic" genes (genes which are associated with more depression) are not always depressogenic, it depends on their environmental context, your gender, your age, and what type of stress you are under".

She added *"We have surveyed more than 1000 people in this research, but this is a fairly modest sample in terms of population genetics, so we are continuing the research to allow us to confirm the findings".*

ENDS

Notes for Editors

Please mention the ECNP Congress in any story resulting from this press release.

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The European College of Neuropsychopharmacology (ECNP)

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The 31st annual ECNP Congress takes place from 6th to 9th September in Barcelona. It is Europe's premier scientific meeting for disease-oriented brain research, annually attracting between 4,000 and 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: https://2018.ecnp.eu/

ABSTRACT: Poster presentation P 847

5-HTTLPR 'social sensitivity' short allele may protect against depression after exposure to social network stressors in young people

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Background: 5-HTTLPR is one of the most investigated genetic polymorphism in interaction with stressful life events in the emergence of depression. Recently we reported that this polymorphism selectively mediates the depressogenic effects of only certain types of stressors, namely financial difficulties [1]. Research also revealed that the "depressogenic" short variant of this gene conveys adaptive characteristics related to social conformity and social cognition-related neurocognitive tasks [2] indicating that it may play a role in adaptation as a 'social sensitivity' allele. In spite of this, no research focused on the possible protective role of this variant against depression in interaction with distinct types of life stressors.

Aims: Our aim was to investigate the effect of 5-HTTLPR in interaction with different types of recent negative life events on current depressive symptoms in a large general European sample in Budapest and Manchester. Since previous results also indicated that the effect of 5-HTTLPR may be age dependent [2], we investigated young people aged 30 years or below.

Methods: Interaction between exposure to 4 distinct types of recent stressors including relationship difficulties, illness/injury, financial difficulties and social network stressors (as measured by the List of Threatening Experiences) and 5-HTTLPR genotype on severity of current depressive symptoms (as measured by the Brief Symptom Inventory, BSI) was investigated in a general population sample of 1081 Caucasian subjects aged 30 years or younger in Manchester and Budapest with linear regression, testing recessive models with population, age, gender and main effect of genotype as covariates. False discovery rate q values with bootstrapping were calculated to correct for multiple testing. Post hoc Mann-Whitney u-tests were used to compare BSI depression scores in subject with different genotypes (ss vs. sl/ll) in groups exposed to different levels of recent stress.

Results: 5-HTTLPR was in Hardy-Weinberg equilibrium in the sample (p=0.77). A significant interaction between 5-HTTLPR genotype and social network disturbances was detected (p=0.0092, q=0.0333), while the interaction was not significant in case of illness/injury (p=0.3781, q=0.2500), relationship difficulties (p=0.6227, q=0.3235) or financial difficulties (p=0.0980, q=0.1182). Post hoc Mann-Whitney u-tests indicated that in case of recent social network stressors, in case of those not exposed to stress ss carriers had significantly higher depression scores (p=0.041) compared to sl/ll carriers, while there was no significant difference in different genotype carriers in case of mild (p=0.351) or severe exposure to social network stressors (p=0.635).

Discussion: Our results indicating that the s allele of the 5-HTTLPR selectively protects against depression when exposed to social network stressors but not other types of negative life events in young people are in line with previous research suggesting that 5-HTTLPR s allele has an adaptive and possibly protective evolutionary role by increasing sensitivity

Please contact the press officer if you need funding information (too much to include here).