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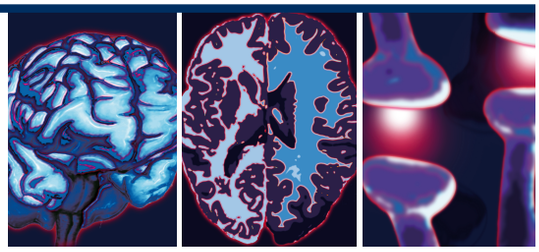

Cannabis use may increase the risk of depression in genetically vulnerable individuals

While numerous studies have established a temporal association between cannabis use and the onset of schizophrenia, few studies have addressed the concept of depression in cannabis-using individuals. An investigation carried out by Roy Otten, first author of the paper published in *Addiction Biology* and researcher from the Behavioural Science Institute of Radboud University Nijmegen (Nijmegen, The Netherlands), has revealed that genetically vulnerable users may increase their likelihood of experiencing depressive symptoms if they use cannabis.

Cannabis usage has become more widespread over the years, with considerable legal differences concerning possession and use in many countries. Epidemiological evidence suggests that approximately 30% of 16-year-olds in The Netherlands have tried cannabis at least once, with 12% stating that they had used it within the last month.

The long-term prospective study followed 428 families (each with two adolescent children) over a period of 5 years. During this time, the investigators measured the adolescents' responses to questionnaires regarding the state of their behavioral and mental health. The results suggested that adolescents with a genetic background predisposing them to an increased chance of depression onset were more likely to develop negative symptoms having used cannabis. The particular serotonin gene in question has been well studied in relation to depression, as the variant that predisposes individuals to the disorder is present within two-thirds of the population.

There have been suggestions that cannabis use may be a result of these individuals attempting to counteract the feelings and effects of depression. Speaking about the study, Otten addresses this issue and further comments on the relevance and importance of the investigation: "The effect is robust. It still remains, even if you take into account a series of other variables that could cause the effect, such as smoking behavior, alcohol use, upbringing, personality and socioeconomic status. Some people might think that young people with a disposition for depression would start smoking cannabis as a form of self-medication, and that the presence of depressive symptoms is therefore the cause of cannabis use. However, in the long term that is definitely not the case."

With the incidence and prevalence of depression on the rise, understanding the numerous genetic and environmental factors that play a role in the disease is an important aspect of research for this highly variable disorder.

– Written by Jonathan Tee

Source: Otten R, Engels RC. Testing bidirectional effects between cannabis use and depressive symptoms: moderation by the serotonin transporter gene. *Addict. Biol.* doi:0.1111/j.1369-1600.2011.00380 (2011) (Epub ahead of print).

Suicidal behavior may be linked to a specific gene

Suicidal thoughts and behavior remain a difficult topic in psychiatry due to the differing approaches to the subject that have been taken over the years in both a medical and social context. Although there have been a number of studies that have investigated the different genetic and environmental contributions to these thoughts, this novel research suggests a strong link between an individual gene and suicidal behavior. The work, published in the *International Journal of Neuropsychopharmacology*, was carried out by researchers from the Centre for Addiction and Mental Health (Toronto, Canada).

Suicide remains a complex topic due to the numerous factors that play a role in its ideation, in addition to the ethical and social implications of the topic. A number of previous studies have implicated brain-derived neurotrophic factor (BDNF) in suicide, as this neurotrophin is responsible for the maintenance and growth of numerous neurons and synapse. Furthermore, alterations to the *BDNF* gene have been linked to other neuropsychiatric diseases such as schizophrenia, depression and dementia.

In this study, the researchers utilized data from their original study on schizophrenia, in addition to 11 other studies with relevant data, to perform a meta-analysis (including 3352 patients, of which 1202 had previous suicidal behaviors) on the available data of the *BDNF* gene in those with a confirmed diagnosis of a psychiatric disorder. The results suggest that individuals with the methionine mutation in the gene were more likely to have a higher incidence of suicidal thoughts and behavior compared with those with the valine genetic variation.

> "Although there have been a number of studies that have investigated the different genetic and environmental contributions to these thoughts, this novel research suggests a strong link between an individual gene and suicidal behavior."

The authors of the paper note that approximately 90% of suicide cases are by individuals with a history of neuropsychiatric complications. Speaking to *Neuropsychiatry* about the impact of the research, James Kennedy, senior author of the paper and director of the Neuroscience Department in the Centre for Addiction and Mental Health, explained that, "The cause of suicidal behavior is complex and not well understood. The work presented in this article helps improve our understanding of the biology underlying suicidal behavior. While our findings are of interest, they only provide a small piece of the puzzle on what causes suicidal behavior. Nonetheless, they encourage additional investigations into the role of BDNF and its signaling partners in the development of suicidal behavior."

The authors go on to explain the possibility of therapeutic intervention in these genetically predisposed individuals, through the creation and application of a compound that would be able to increase BDNF functioning. Clement Zai of the Centre for Addiction and Mental Health goes on to explain that, "Our findings may lead to the testing and development of pharmacological agents that target this gene to reduce the risk of suicide in susceptible individuals. In the future, if other researchers can further replicate and extend our findings, then genetic testing may be possible in helping to identify individuals at increased risk for suicide. In addition to genetic factors, environmental risk factors, including and not limited to early childhood trauma, recent life stress, alcohol abuse and substance abuse, should be taken into consideration while assessing suicide risk."

– Written by Jonathan Tee

Source: Zai CC, Manchia M, De Luca V *et al.* The brain-derived neurotrophic factor gene in suicidal behaviour: a meta-analysis. *Int. J. Neuropsychopharmacol.* doi:10.1017/S1461145711001313 (2011) (Epub ahead of print).

Behavioral therapies demonstrate promise in post-traumatic stress disorder patients

A new study published in the *Archives of General Psychiatry* has investigated the benefits of a number of behavioral therapies on post-traumatic stress disorder (PTSD). The research, carried out by Arieh Shalev and colleagues from the Hadassah University Hospital (Israel), compared a number of interventions for the treatment of PTSD, including early- and delayed- exposure-based treatment and cognitive and pharmacological interventions. Early- and delayed-exposure-based treatment and cognitive–behavioral therapy all demonstrated effectiveness in reducing stress disorder symptoms in new sufferers of PTSD.

PTSD is an anxiety disorder that develops after the occurrence of psychological trauma. The presentation of patients is variable, but includes nightmares, flashbacks of the event and avoidance of a particular trigger.

Participants were recruited from the Hadassah University Hospital from consecutively admitted patients of traumatic events. Patients displaying acute stress disorder during the interview were invited to participate in the study. These participants were randomly assigned to one of four groups: prolonged-exposure therapy;

cognitive–behavioral therapy; selective serotonin-reuptake inhibtor/placebo interventions, or the waiting list control group. The impact of these interventions were measured using the Clinician-Administered PTSD Scale (CAPS), a standardized test to determine PTSD severity.

At 5 months, the cognitive–behavioral therapy group and the prolonged-exposure therapy group had incidences of PTSD of 18.2 and 21.4%, respectively. This was shown to be significantly lower than the waiting list control group and the selective serotonin-reuptake inhibtor/placebo groups (58.2, 61.9 and 55.6%, respectively).

The findings suggest the potential benefit of behavioral interventions in this population, in addition to the required timings of these treatments. Shalev explained to *Neuropsychiatry* the significance of the work: "We think that this work is important in that it reasserts the importance of evidence-based interventions (both prolonged exposure and cognitive therapy) provided to identify and carefully assess survivors of traumatic events (in this work – only to those who met the full PTSD diagnostic criteria) within the first few months following traumatic incident hostilities."

"Early- and delayed-exposure-based treatment and cognitive–behavioral therapy all demonstrated effectiveness in reducing stress disorder symptoms in new sufferers of PTSD."

Furthermore Shalev went on to explain the potential for this work in future studies: "We would love to see it practiced in those clinical settings that have access (or can create access) to survivors of recent traumatic events. Given the disabling and unremitting nature of chronic PTSD, we would like to think that this paper should encourage healthcare providers to approach and treat those with typical symptoms of acute PTSD within the window of opportunity of the first few months after trauma exposure."

– Written by Jonathan Tee

Source: Shalev AY, Ankri Y, Israeli-Shaley Y, Peleg T, Adessky R, Freedman S. Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach and Prevention study. *Arch. Gen. Psychiatry* doi:10.1001/archgenpsychiatry.2011.127 (2011) (Epub ahead of print).

Dopaminergic gene variants may increase the efficacy of ADHD medication

Methylphenidate is the most commonly prescribed pharmacological agent for the treatment of ADHD. However, recent research published in the *Journal of the American Academy of Child and Adolescent Psychiatry* has suggested that certain genetic variants in patients may explain the increased response to the medication in some individuals compared with others.

The study involved 89 children with ADHD between 7 and 11 years of age. Certain genetic variants of the dopamine transporter and D_4 receptor increased the response to methylphenidate, resulting in improved behavior in these individuals. Speaking about the importance of the work, Tanya Froehlich, first author of the paper and researcher at Developmental and Behavioral Pediatrics at Cincinnati Children's Hospital Medical Center (OH, USA) explained: "With more information about genes that may be involved in ADHD medication response, we may be able to predict treatment course, tailor our approach to each child and improve symptom response while decreasing healthcare costs."

The work marks the first instance of a placebo-controlled pharmacogenetic trial of ADHD in children looking at these specific genetic variants. The participants were given either methylphenidate or a placebo and their behavior and response was measured using recordings from their parents and teachers. Saliva samples were taken for genetic testing in order to ascertain the genetic variants the children had. Those without the 'ten-repeat' variant of the dopamine transporter gene demonstrated a greater response to methylphenidate, compared with those without this variant. On the other hand, those with the 'four-repeat' variant of the *DRD4* receptor gene showed a greater response to the medication than those without this variation.

The work provides a clear example of the importance of pharmacogenetics in the field and may provide more effective diagnostic measures of medication benefit in an ever-growing population.

– Written by Jonathan Tee

Source: Froehlich TE, Epstein JN, Nick TG *et al.* Pharmacogenetic predictors of methylphenidate dose–response in attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 50(11), 1129.E2–1139.E2 (2011).

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