European College of Neuropsychopharmacology – press release

Doctors develop system which can predict Bipolar Disorder 4 years before onset

Embargo until: 00.05 CEST (Vienna) Tuesday 15th September 2020

Type of study: peer-reviewed/observational study/people

An international team of doctors have developed a machine learning system which can predict the development of Bipolar Disorder up to 4 years before onset in young people: at age 18 it was able to predict which individuals would develop the condition at age 22. This work is presented at the ECNP virtual congress, and is in press with a peer-reviewed journal*(See below).

"*This maybe a new additional tool for the diagnosis of bipolar disorder; this will not replace a doctor's diagnosis, but may allow them to take preventative measures to slow or avoid the onset of the condition, and so gain 4 years of preventative treatment*" said lead researcher Francisco Diego Rabelo-da-Ponte.

The researchers, from Brazil, Canada and the USA, followed 3810 individuals born in Pelotas, Brazil, in 1993, taking measurements and interviews at the ages of 11, 15, 18 and 22. The study was looking at general health from birth, but has had a particular application in mental health. At the end of the 22 year follow up, 255 of the people in the study (6.7%) had received a diagnosis of bipolar disorder.

Lead researcher Francisco Diego Rabelo-da-Ponte, from the Federal University of Rio Grande do Sul, Brazil said:

"*What we found was that we can identify who will develop bipolar disorder around four years before the onset of the condition, by tracking the individuals from birth through to adulthood. We used machine learning techniques which are based on the same learning techniques used to detect such things as spam and weather forecasting.*

There were several factors which tended to point to a greater risk for bipolar disorder, For example if 18 year olds show more suicidal tendency, general anxiety, evidence of parental physical abuse, and financial problems, then they may have been at greater risk. It was the job of the machine learning to weigh these factors and estimate the risk of developing bipolar disorder".

Bipolar disorder is estimated to be the sixth cause of disability in the world, however, its proper identification still frequently represents a challenge, with an average delay of six years between first symptoms and formal diagnosis. Additionally, only 20% of people with bipolar disorder and presenting with a depressive episode are diagnosed with bipolar

disorder within the first year of seeking treatment. Diagnostic and treatment delays have harmful consequences for the clinical course of illness, for example, greater severity of symptoms, shorter time between episodes of mood, cognitive and functional impairment. Identifying bipolar disorder early is a growing interest because many patients are mistreated and misdiagnosed, avoiding the progression of the disease.

Francisco Diego Rabelo-da-Ponte said:

"I*t's very difficult and expensive to replicate such a long-lasting study, but what we have found indicates that we need more of these longitudinal studies. We've already learned a lot from the study itself, for example if we were to set it up now we would include many more mental health parameters, which we hope would allow us to identify even more psychological benefits. We see too many false positives (indicating someone is at risk when they are not) to rely 100%% on this system alone. Nevertheless, this system will allow doctors to see who might be at risk, and the gain of 4 years before diagnosis could make a huge difference to the life of a young person*".

Commenting, Professor Eduard Vieta (Barcelona), ex-ECNP Executive Committee member said:

"*Population-based cohort studies are extremely important to develop predictive models that may aid in the prevention of serious conditions such as bipolar disorder. There have been other initiatives in the past to build calculators with that aim. What is most needed is replication and verification of the validity of the algorithm. The present study, hence, has its merits but is relatively small and needs replication in a separate, independent cohort; moreover, unusual findings such as the underrepresentation of bipolar II disorder need clarification as well*."

This is an independent comment; Professor Vieta was not involved in this work.

* Publication details: **Early identification of bipolar disorder among young adults – a 22 year community birth cohort**, Francisco Diego Rabelo-da-Ponte, Jacson Gabriel Feiten, BensonMwangi, Fernando C. Barros, Fernando C. Wehrmeiste[5], Ana Maria Menezes, Flavio Kapczinski,Ives Cavalcante Passos, Mauricio Kunz[3]. In press *Acta Psychiatrica Scandinavica* (September 2020), DOI 10.1111/acps.13233
Journal website https://onlinelibrary.wiley.com/journal/16000447?tabActivePane=

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Notes for Editors

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 33rd annual ECNP Congress takes place from 12th to 15th September. It is Europe's premier scientific meeting for disease-oriented brain research. In 2020 it is a virtual congress. The regular congress annually attracting up to 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: https://www.ecnp.eu/Congress2020 The 2021 congress is scheduled to take place in Lisbon next September.

Conference abstract P.250 Prediction of bipolar disorder four years before onset in a 22-year population-based birth cohort using advanced machine learning techniques

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Background. Bipolar disorder (BD) is the sixth leading cause of disability worldwide. There is an average delay of 10 years between first symptoms and formal diagnosis of BD. Prediction of BD may help clinicians to intervene early and to prevent illness progression.

Aim. We sought to build a BD prediction model using machine learning techniques in a large population-based birth cohort at the individual level.

Methods. A total of 3,748 subjects were studied from birth up to the age of 22 years in a prospective population-based birth cohort. The authors used the Elastic Net algorithm with 10-fold cross-validation to predict who would develop BD by the age 22-years assessment using clinical and demographic variables at each follow-up visit before diagnosis (perinatal, 11 years, 15 years, and 18 years). After that, it was used the best predictive model to calculate the subgroups of subjects at higher and lower risk of developing BD and analysed the clinical differences among them. Furthermore, we performed the permutation test shuffling the outcome 1,000 times with the best predictive model. Lastly, we calculated the estimation error of cross-validation with the best predictive model using different splits and cross-validation methods.

Results. A total of 107 (2.8%) individuals within the cohort presented with BD type I, 26 (0.6%) presented with BD type II, and 87 (2.3%) presented with BD not otherwise specified. The models presented the following measures: 1) perinatal follow-up visit: balanced accuracy 0.58, sensitivity 0.6, specificity 0.57, positive predictive value (PPV) 0.09, negative predictive value (NPV) 0.95, area under the ROC curve (AUC) 0.62 (confidence interval [CI] 0.55–0.69); 2) 11-years follow-up visit: balanced accuracy 0.59, sensitivity 0.52, specificity 0.66, PPV 0.10, NPV 0.95, AUC 0.64 (CI 0.55–0.72); 3) 15-years follow-up visit: balanced accuracy 0.56, sensitivity 0.49, specificity 0.64, PPV 0.09, NPV 0.94, AUC 0.61 (CI 0.52–0.70); 4) 18-years follow-up visit: balanced accuracy 0.75, sensitivity 0.72, specificity 0.77, PPV 0.18, NPV 0.97, AUC 0.82 (CI 0.75–0.88). Only at the 18-years follow-up visit was the algorithm able to predict who will develop BD at 22 years of age. The most important variables to predict BD at the 18-years follow-up visit were suicide risk, a diagnosis of generalized anxiety disorder, parental physical abuse, and financial problems. Additionally, the high-risk subgroup of BD showed a high frequency of drug use and depressive symptoms. Additionally, we compared the distribution of random rearrangement permutation of the outcome with the original dataset, using 1,000 permutations. We verified a statistical difference between the original model and permutation models ($p<0.001$), which means that the predictive model using the 18-years follow-up visit to predict who will develop BD at 22 years of age is not random. Our model exhibited low estimation error (mean [SD], 0.04[0.01]).

Conclusions. We developed a machine learning-based risk calculator for BD at the age of 22 years, which may be used as a tool for clinical decision making, incorporating both demographic and clinical variables. Furthermore, pre-morbid symptoms and environmental stressors were important predictors of BD four years before the onset of the disorder.

Funding: This work is based on data from the study "Pelotas Birth Cohort – 1993" conducted by Graduate Program in Epidemiology at Universidade Federal de Pelotas with the collaboration of the Brazilian Public Health Association (ABRASCO). Furthermore, the 1993 birth cohort study was supported by the Wellcome Trust (72403MA, 086974/Z/08/Z), Brazilian National Research Council (CNPq) with Brazilian Ministry of Health – DECIT &CNPq (400943/2013-1), National Institute for Science and Technology – Translational Medicine (INCT-TM) (2014/50891-1 – FAPESP; 465458/2014-9 - CNPq).