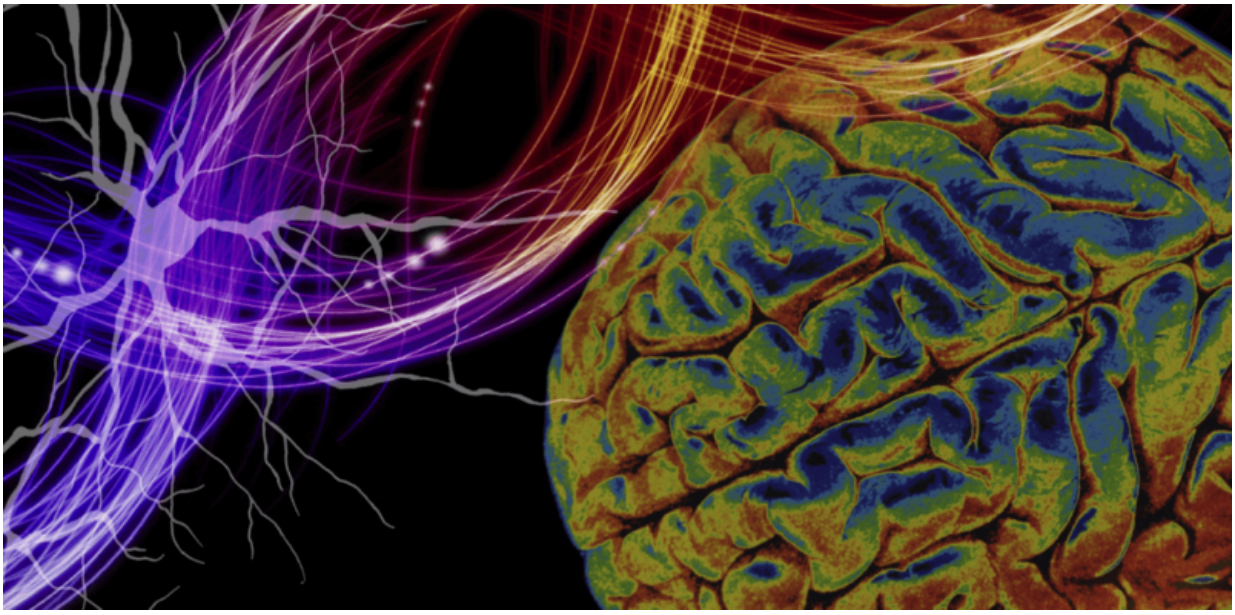
Connecting genetic variations to schizophrenia and other mental illnesses

May 5 2016, by Rachel Jonas



Credit: Therese Vesagas, CC BY

We know that changes in our genetic code can be associated with an increased risk for psychiatric illnesses such as schizophrenia and bipolar disorder. But how can a genetic mutation lead to complex psychiatric symptoms such as vivid hallucinations, manic episodes and bizarre delusions?

To find out, researchers are trying to fill in the blanks between the

genetic blueprint (genotype) and psychiatric disorder (psychiatric phenotype). Phenotypes a set of observable characteristics that result when a particular genotype interacts with its environment. The phenotype is the eventual outcome of a specific genotype.

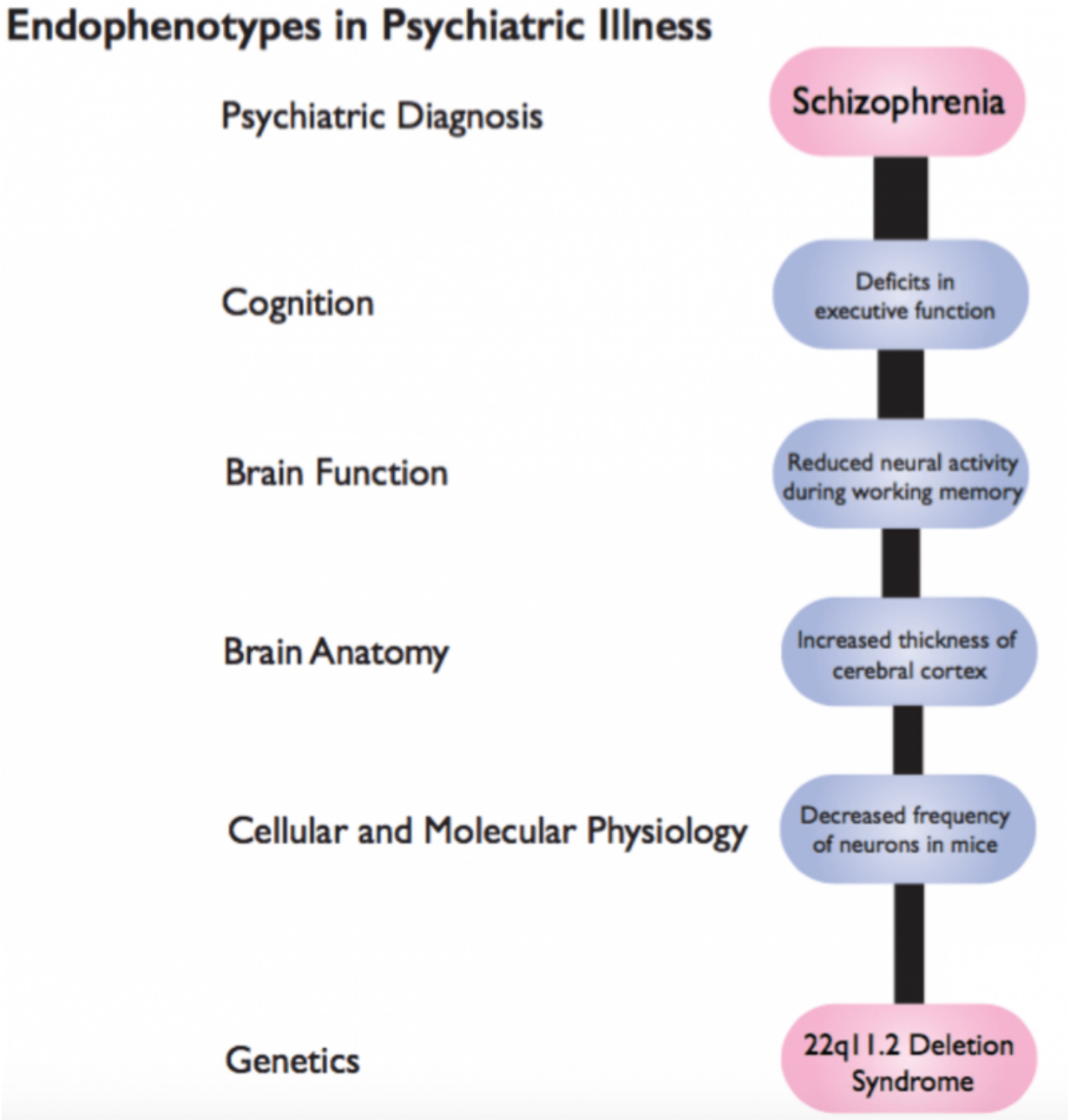
But between genotype and psychiatric phenotype lie many measurable traits that together are called endophenotypes. This is an aspect of genetics that scientists are just starting to understand.

The National Institute of Mental Health has recently begun an initiative to push researchers to study endophenotypes with a program called Research Domain Criterion (RDoC), described as an effort to study basic dimensions of functioning that underlie human behavior.

So what exactly are endophenotypes, and how might they contribute to psychiatric illnesses?

Endophenotypes lie between genes and psychiatric phenotypes

An endophenotype can refer to anything from the size and shape of brain cells, to changes in brain structure, to impairments in working memory. The term can refer to a physical trait or a functional one.



The links leading from genetic alterations to psychiatric illness in 22q11.2 Deletion Syndrome. Credit: Rachel Jonas, CC BY

An endophenotype must be associated with a specific psychiatric illness, such as schizophrenia, and it must be heritable. It must also be present

even if the illness is not active. Within families, the endophenotype must be more common in ill family members than in healthy family members. But the endophenotype must be more common among nonaffected relatives of people with the associated illness than among the general population.

Certain endophenotypes are thought to precede behavioral symptoms. For instance, in several conditions, such as schizophrenia and Alzheimer's disease, changes in brain structure have been found years before the onset of symptoms.

Currently doctors diagnose a psychiatric disorder based on the patient's symptoms. The underlying neurobiology isn't usually considered, because we lack the data to really use it.

In the future, endophenotypes might let us detect who is susceptible to psychiatric illness before clinical symptoms develop. That means we could try to combat, or at least appease, the symptoms of the disorder before they start. And knowing how endophenotypes contribute to these disorders could lead to precision medicine treatments.

How do you study endophenotypes?

One way to study the endophenotypes is to focus on a specific genetic alteration that is associated with a psychiatric disorder. This way we can get a sense of what brain changes the genetic change causes.

For instance, I study a genetic disorder called 22q11.2 Deletion Syndrome (also called 22q11DS). The syndrome is due to a deletion of up to 60 genes, many of which are linked to brain function. About 30 percent of individuals with 22q11DS will develop schizophrenia (the rate in the U.S. population overall is about one percent).

Credit: CC0 Public Domain

Studying 22q11DS lets us draw a line from a genetic alteration to a psychiatric phenotype, such as decreased neural function, brain structure changes or fewer neurons in certain parts of the brain, and to a psychiatric phenotype, such as schizophrenia.

Let's go through some concrete examples of how this can be done.

22q11DS: a model syndrome to study endophenotypes

In one study researchers looked at a group of 70 children and adolescents

with 22q11DS, and found deficits in executive function (which encompasses cognitive processes such as motivation, working memory and attention) in patients with 22q11DS.

In fact, researchers were actually able to *predict* subsequent development of psychotic symptoms in individuals with 22q11DS. This study shows that cognitive endophenotypes may underlie psychiatric phenotypes and demonstrates their predictive power. And, like all endophenotypes, it is invisible to the naked eye, but measurable in the lab.

Another study, using functional magnetic resonance imaging (fMRI), found reduced neural activity in patients with 22q11DS when they performed a working memory task compared to a group of healthy control subjects. What's more, the magnitude of the decrease correlated with the severity of their psychotic symptoms. This suggests abnormalities in neural activity might underlie symptoms associated with schizophrenia.

Other studies have found an association between psychiatric illnesses such as schizophrenia and abnormalities in the size and shape of different brain regions. For instance, a recent study found that certain parts of the brain were thicker in patients with 22q11DS. What's more, the degree of thickness was related to psychotic symptoms. Changes in brain structure have also been associated with psychiatric disorders, such as obsessive compulsive disorder.

In order to gain a more in-depth understanding of the underlying physiology in 22q11DS, researchers can breed mice with the deletion syndrome by "knocking out" genes in the mouse genome.

Researchers have found that mice with 22q11DS had fewer neurons in a part of the brain associated with cognition compared to unaffected mice.

The number of neurons correlated with how well the mice performed on tasks measuring executive function. These results suggest that individuals with psychiatric illnesses might actually have microscopic changes in their brain cells. This is a significant finding, because we can't study these effects directly in humans.

These are just some examples of how we can experimentally determine endophenotypes that underlie schizophrenia in 22q11DS. And while 22q11DS is a risk factor for schizophrenia, what we learn form studying this syndrome could help us understand the endophenotypes behind other illnesses.

Of course defining endophenotypes for psychiatric illness is just the first step. After that, researchers and scientists need to find ways to use these results to inform diagnosis, treatment and prevention strategies.

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