# Chapter 15 Diathesis Stress Models (also known as Gene-Environment Interaction

Depression is among the top five leading causes of disability and disease burden throughout the world. Across the life span, stressful life events that involve threat, loss, humiliation, or defeat influence the onset and course of depression. However, not all people who encounter a stressful life experience succumb to its depressogenic effect. Diathesis-stress theories of depression predict that individuals' sensitivity to stressful events depends on their genetic make-up . Behavioral genetics research supports this prediction, documenting that the risk of depression after a stressful event is elevated among people who are at high genetic risk and diminished among those at low genetic risk.

However, whether specific genes exacerbate or buffer the effect of stressful life events on depression is unknown. In the study that follows (Caspi, 2003), a functional polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*) was used to characterize genetic vulnerability to depression and to test whether 5-HTT gene variation moderates the influence of life stress on depression.

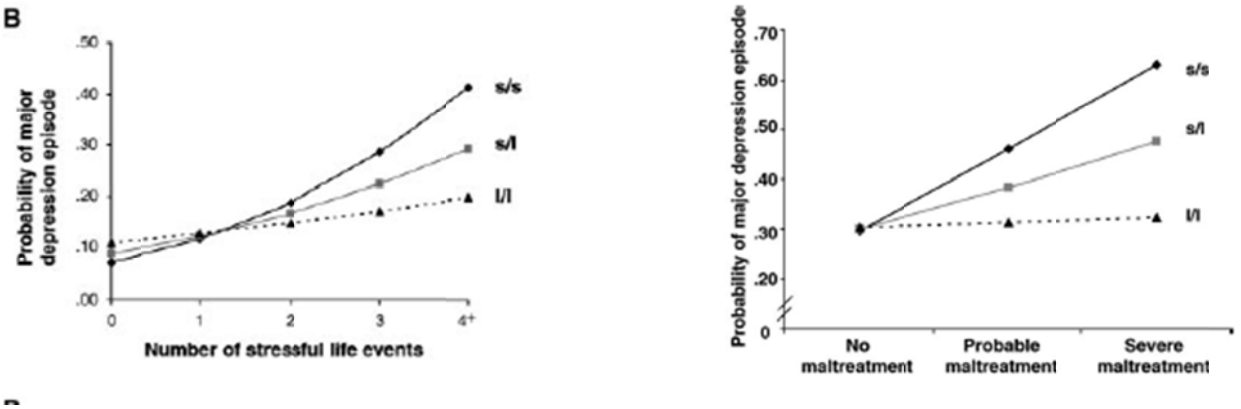
The serotonin system provides a logical source of candidate genes for depression, because this system is the target of selective serotonin reuptake–inhibitor drugs that are effective in treating depression. The serotonin transporter has received particular attention because it is involved in the reuptake of serotonin at brain synapses. The short ("s") allele in the 5-HTTLPR is associated with lower transcriptional efficiency of the promoter compared with the long ("l") allele.

(The authors provide evidence that the long/short alleles have something to do with risk for stress in rats, monkeys, and humans.)

A representative birth cohort of 1037 children (52% male) has been assessed at ages 3, 5, 7, 9, 11, 13, 15, 18, and 21 and was virtually intact (96%) at the age of 26 years. Stressful life events occurring after the 21st birthday and before the 26th birthday were assessed with the aid of a life-history calendar.

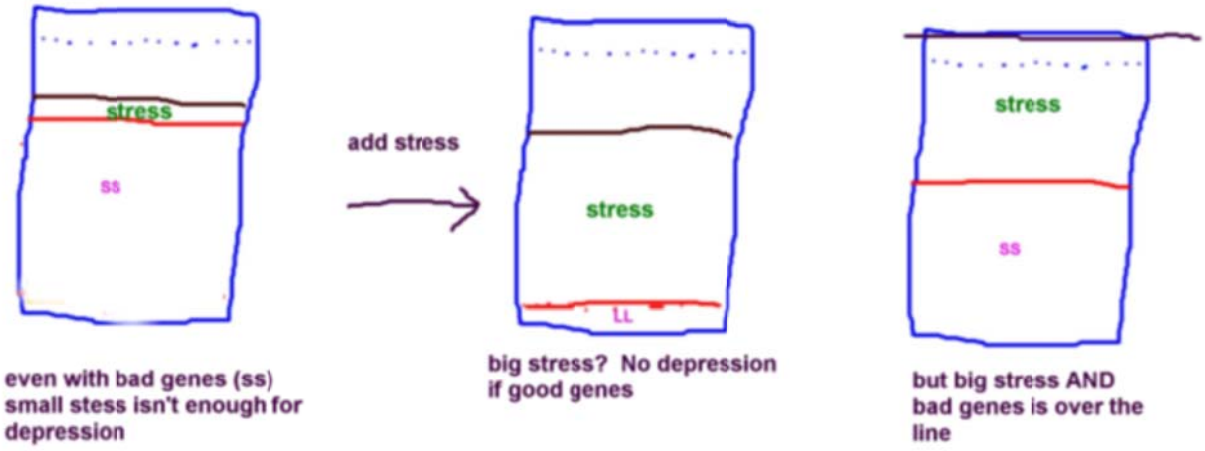
Study members were assessed for past-year depression at age 26 with the use of the Diagnostic Interview Schedule, which yields a quantitative measure of depressive symptoms and a categorical diagnosis of a major depressive episode according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

The G x E interaction showed that stressful life events predicted a diagnosis of major depression among carriers of an s allele but not among l/l homozygotes ($P = 0.056$, Fig. 1B).




In other words look at the two figures and ask: If you have good genes (LL alleles), will stress affect you and make you depressed? What if you have poorer genes (ss alleles)?

# Caspi as a Diathesis-Stress Model




Think of a diathesis-stress model as a glass. You put in both the genetic vulnerability and the environmental stress. If they add together to be above the dotted line, then you will express the disorder. You can see it takes a combination of both genes and environment to express a disorder.

We can think of Caspi's study as an example of a diathesis-stress model. The genetic vulnerability is the short alleles (ss). The glass at the left shows high genetic vulnerability because you can see the region of "ss" is big. But with minimal stress from the environment, you don't get depressed. Together the inherited vulnerability (predisposition) and the stress isn't enough to push the volume over the line.

The middle glass shows minimal genetic vulnerability but much more stress. Even so, together they don't add up to above the line.

The glass on the right, however, shows a good amount of inherited vulnerability (big region of "ss"), and enough stress from the environment to push you over the dotted line. You will express the disorder with the glass on the right.