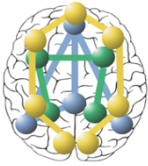


## Personalized brain circuit biotypes

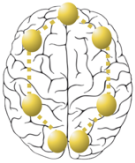
**Source:** Tozzi, L., Zhang, X., Pines, A. *et al.* Personalized brain circuit scores identify clinically distinct biotypes in depression and anxiety. *Nat Med* (2024). <https://doi.org/10.1038/s41591-024-03057-9>  
Supplemental Table 16 for additional details.

### $D_{C+S_C+A_{C+}}$ 'Default with salience and attention hyperconnectivity'



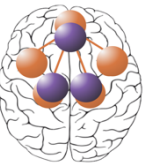
The  $D_{C+S_C+A_{C+}}$  biotype was distinguished by intrinsic hyper-connectivity of the default mode as well as salience and attention circuits. This biotype had slowed responses when processing negative emotions, consistent with a negative bias. During cognitive tasks, this biotype also had slowed responses while sustaining attention and made fewer errors when suppressing irrelevant information, indicating caution rather than impulsivity, and consistent with the involvement of the frontal parietal attention circuit. However, during more demanding executive function task, they tend to make more errors. This biotype was associated with better responses on behavioral talk therapy.

### $A_C$ 'Attention hypoconnectivity'



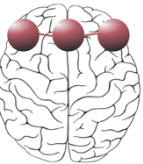
The  $A_C$  biotype was distinguished by reduced intrinsic connectivity within the attention circuit. This biotype had less severe symptoms of tension. They made more errors during a sustained attention task requiring concentration and was faster to respond in a cognitive task requiring suppression of interfering information, indicative of less impulse control. This biotype was not responsive to behavioral talk therapy and may require a different treatment.

### $NS_{A+P_{A+}}$ 'Sad-elicited negative affect with positive affect hyperactivation'



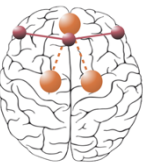
The  $NS_{A+P_{A+}}$  biotype is distinguished by over activity in regions of affective brain circuits that process emotional stimuli. This biotype is associated with symptoms of ruminative brooding on negative thoughts and anhedonia, which is the inability to experience pleasure.

### $C_{A+}$ 'Over activity in cognitive regions of the brain'



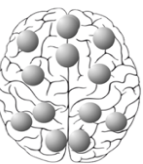
The  $C_{A+}$  biotype is distinguished by over activity in the Cognitive Control circuit of the brain. This biotype is associated with more severe symptoms of negative bias (hopelessness, pessimism), threat dysregulation (difficulty managing fears), anhedonia (inability to feel pleasure) and anxious arousal (physical signs of anxiety). This biotype makes more errors on cognitive tasks requiring executive function, control of irrelevant information and sustained attention. Executive function is slowed. This biotype responded best to the antidepressant venlafaxine (Effexor).

### $NTC_{C-C_{A-}}$ 'Cognitive control hypoactivation with conscious threat-elicited negative affect hypoconnectivity'



The  $NTC_{C-C_{A-}}$  biotype is distinguished by lower activity in regions of the cognitive control circuit during a control task that requires inhibition of irrelevant information, as well as reduced connectivity during the processing of threat-related negative emotions. This biotype profile reflects difficulty in the brain's executive control functions and in regulating emotion. This is a target biotype for different types of treatment in new studies currently underway.

### $D_X S_X A_X N_X P_X C_X$ 'Intact activation and connectivity'



The  $D_X S_X A_X N_X P_X C_X$  biotype was not distinguished by specific circuit dysfunction in this study. However it was clinically characterized clinically by more pronounced implicit biases toward threat-related stimuli. Future studies will explore if additional brain regions are involved.

**Legend for technical biotype labels:** The first character in the technical biotype label refers to which brain circuit showed a dysfunction. The first subscript character refers to the type of dysfunction: either an activity dysfunction (A) or a connectivity dysfunction (C). Activity refers to how an individual part of the brain responds to a certain task. Connectivity refers to how different parts of the brain work together in the task. The subscript sign refers to whether the dysfunction was "too high" (+) or "too low" (-). The technical biotype label is given by the overall combination of dysfunctions. So, for example,  $NTC_{C-C_{A-}}$  is a biotype characterized by lower than normal connectivity ( $C_{-}$ ) in the threat circuit elicited by non-conscious threat (NTC) and, in addition to that, lower than normal activation ( $A_{-}$ ) in the cognitive circuit in response to a cognitive task (C).