

Appendix 1 (as supplied by authors):

Current conceptions view the etiology and maintenance of major depressive disorder as the result of a complex interplay between neurotransmitter aberrations, structural neuroanatomic differences and dynamic metabolic disturbances in mood generating neural circuits, all of which are likely inherited (Appendix Figure 1)<sup>1</sup>. These circuits connect top-down processing centers, such as those involved in conscious cognition and perception, with bottom-up modulatory centers, such as those involved in generating autonomic and unconscious influences on behaviour. The normal functioning of this system is crucial to its flexibility, which manifests in an ability to respond to diverse situations by regulating one's mood. In major depressive disorder, these circuits are dysfunctional, with disordered activation in some structures, such as the subcallosal cingulate and amygdala, leading to a perpetual dysphoric state. The mechanisms underlying circuit dysfunction in depression are heterogeneous and diverse and may indeed involve different neurotransmitter systems and poly-synaptic networks, corresponding to the different symptoms of the illness. For example, neuroimaging studies have found that networks subserving cognitive control, affective regulation, and self-reflection, all of which are dysfunctional in depression, significant overlap in the region of the anterior cingulate, suggesting the importance of that structure in Major Depressive Disorder<sup>2</sup>. Psychotherapeutic and pharmacologic strategies, which target specific thought patterns or neurotransmitter systems, respectively, can often be used to correct the activity within mood circuits but in a substantial proportion of patients these strategies are ineffective. Current neuromodulation strategies attempt to take advantage of known circuit models in order to modulate activity in key structures and influence the functioning of the broader mood circuit. The clinical effect observed may as a result be mediated by a different mechanism than conventional

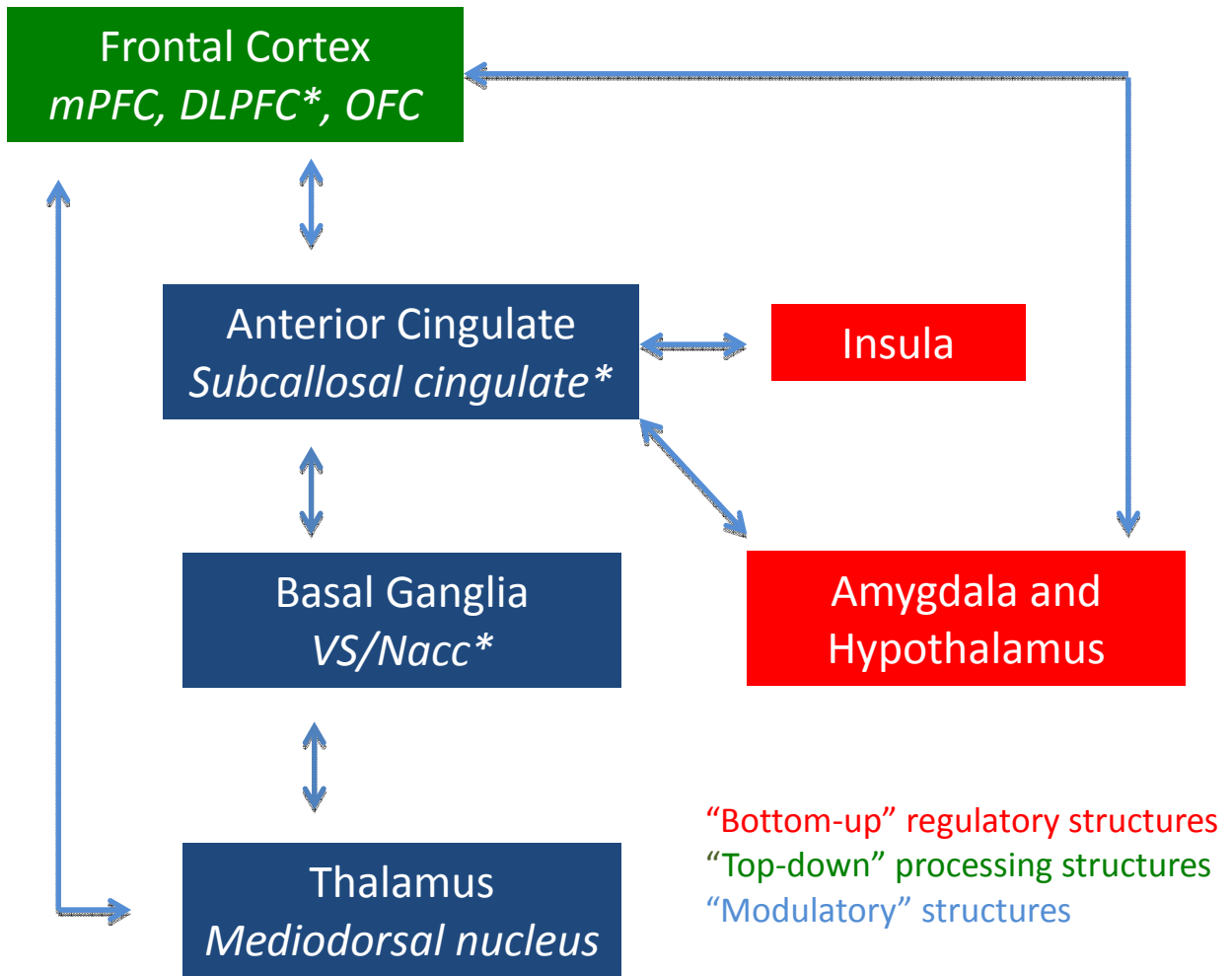
pharmacologic treatment, thereby providing a direct means to ‘reset’ the activity of dysfunctional mood circuits.

#### Appendix Figure 1 Legend

Key anatomic structures comprising mood and affective regulation circuitry. Structures involved in cognitive (“top-down”) processes (OFC, DLPFC), project to both “modulatory” structures, such as those involved in reward and affective regulation, as well as to autonomic (“bottom-up”) structures (amygdala, hypothalamus). These pathways and the relative contribution of different structures to overall mood circuit dysfunction, account for the often heterogeneous nature of clinical depression. For example, anhedonia and reward processing abnormalities may be traced to nucleus accumbens dysfunction, whereas psychomotor symptoms and endocrinologic disturbance, to autonomic dysfunction. Structures marked with an asterisk have been investigated as targets for focal neuromodulation. mPFC: medial prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; OFC: Orbitofrontal cortex; VS/NAcc: Ventral striatum/Nucleus accumbens.

#### Appendix References

1. Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology*. 2010 Jan;35(1):192-216
2. Sheline YI, Price JL, Yan Z, et al. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A*. 2010 Jun 15;107(24):11020-5.



\*Target of neuromodulation