

## Neurodevelopment and Onsets of Mental Illness including Depressions

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Adolescence is a critical stage in the life course when approximately half of all adult mental illnesses emerge<sup>1</sup>, with clinical depressions comprising the greatest incidence risk, yet we still know very little about how or why this occurs. Theories include psychosocial acceleration, epigenetic and genetic vulnerability, differences in the timing and rates of development occurring across regions of the brain (heterochronicity), dual-process models, and a glucocorticoid vulnerability cascade linked to early life stress. Does one of these theories better explain onsets of (i) episodic and (ii) sex-differentiated mental illnesses, including depressions, (iii) occurring in adolescence? We argue no and that, more likely, a confluence of these theories may be best when attempting to explain each of these three perplexing aspects of mental illness.

Adolescence is a period of rapid brain and psychosocial development. Psychosocial acceleration theory suggests that the timing of hormonal maturation varies as a function of an individual's responsiveness to their rearing environment (via genetic or epigenetic mechanisms) and rearing environment stability<sup>2</sup>. Unstable environmental rearing conditions are associated with unpredictability and uncertainty, which induces greater stress in an individual. Unstable environments therefore require greater adaptation by an individual and have been suggested to accelerate maturation in some, rendering those individuals vulnerable to the development of mental illnesses such as depression<sup>3</sup>. Indeed, a positive relationship between pubertal timing and self-reported depression in a large population sample of adolescents has been observed<sup>4</sup>, but pubertal acceleration alone does not explain how the 1:1 female:male depression incidence ratio in childhood becomes 2:1 in adolescence and adulthood<sup>5</sup>? Gender socialization may account for sex differences in both rates of illness<sup>6</sup> and neurodevelopment<sup>7</sup>. For example, in instances of domestic abuse over which one has minimal control, female

adolescents may favor socializing with delinquent peers over time spent at home more often than male adolescents<sup>6</sup>. Repeatedly experienced across development, these socialization differences may, in part, account for neurodevelopmental sex differences<sup>7</sup>. Additionally, changes in primary caregiver, parental absence, or the introduction of a step-parent, are examples of rearing environment changes that may also partly explain age-related effects of mental illness. Considered together, sex and age may independently as well as interactively influence regional brain development<sup>8</sup>, and increase the proneness of some individuals for developing mental illnesses in adolescence.

Biological sex is associated with different rates of development in different brain regions<sup>8</sup>. Epigenetic regulation of gene expression in the brain may therefore occur in both a sex- and age-specific manner<sup>9,10</sup>. In female mice only, exposure to repeated bites by a larger, more aggressive mouse of the same sex has been shown to amplify social withdrawal behavior and increase brain-derived neurotrophic factor (BDNF) protein in the bed nucleus of the stria terminalis<sup>11</sup>, a region of the brain associated with environmental vigilance<sup>12</sup>. BDNF protein is important for neurodevelopment. Down-regulated BDNF gene expression in the rodent hippocampus, induced by prenatal toxin exposure, has been associated with alterations in both brain function and behavior<sup>10</sup>. A similar effect has been observed in humans, where it has been shown that prenatal exposure to environmental toxins leads to *sex-specific* alterations in DNA methylation of BDNF. Hypermethylation of hippocampal BDNF could therefore function as a biomarker for early-life adversity<sup>10</sup> and partly explain sex- and age-differential rates of mental illness.

While little is known about how gene-environment relationships influence human neurodevelopment and onsets of mental illness, there is some evidence that genes help to tune adolescent development. Twin studies demonstrate differential genetic effects being greater in adolescence than childhood for the onset of depression<sup>13</sup> indexing an additional pathway for sex- and age-differentiation of mental illness, as it is possible that such genes also influence adolescent brain development. These gene and gene-

environment relationships remain to be fully clarified and incorporated into a neurodevelopmental framework.

Human brain development is heterochronic, meaning that different developmental timings and rates of change are observed across regions<sup>14</sup>. Some researchers propose that atypical brain maturation, in combination with psychosocial, environmental and biological factors, predisposes adolescents to different forms of psychopathology, including major depressive disorder (MDD)<sup>15</sup>. More recently, neuroimaging analysis techniques have been applied that concentrate on the coordinated development of *neural systems* distributed across neighboring and distal brain regions<sup>16</sup>. When applied to the aberrant brain maturation hypothesis<sup>15</sup>, disparities in the timing or rate of synapse formation within neural systems, in combination with psychosocial, environmental and biological factors, may confer an increased susceptibility for onsets of mental illness, with depression, drug addictions and psychoses being particularly liable in adolescence and early adulthood<sup>1</sup>.

Compatible with the heterochronic development of neural systems, dual-process models propose that “hot” and “cold” systems underlie both typical and atypical human behavior<sup>17,18,19</sup>. Hot and cold systems were initially proposed to underlie emotionality and cognition, respectively, with their interplay comprising a skillset used by humans during the exertion of willpower<sup>18</sup>. The balance between hot and cold systems is driven by a set of factors, including developmental level, personal history, stress and temperament, and can be further modulated by pharmacological intervention<sup>18, 19</sup>. A developmental imbalance between hot and cold systems is present in adolescence whereby a mature “hot” system occurs alongside a relatively immature “cold” system<sup>1,17</sup>. For example, the hot system’s amygdala, a limbic region involved in the perception of biologically relevant socio-emotional information<sup>20</sup>, matures earlier than the cold system’s hippocampus and prefrontal cortex, regions implicated in memory and cognitive regulation of socio-emotional stimuli, respectively<sup>18,19,21,22,23</sup>. Some researchers therefore suggest that exaggerated neurodevelopmental imbalances between the reflexive “hot” system and the reflective “cold” system contribute to the emergence of affective disorders in adolescence<sup>17</sup>.

One must exhibit caution when assigning hot and cold nomenclature to neuropsychological tasks, as individuals with depressions may exhibit an increased sensitivity to feedback on task performance, thereby instilling negative expectations and a reinterpretation of the cold cognitive task as a hot emotional task<sup>19</sup>. Unfortunately, “cold turned hot” thinking patterns are difficult to change, even with medication or targeted brain stimulation techniques<sup>19</sup>. Repeated “cold turned hot” experiences in addition to early life stressors such as rearing environment instability or chronic psychosocial difficulties could promote accelerated development of the hot system by prompting over-activity and strengthening of connections between “hot” regions. Experientially, this can leave depressed adolescents bewildered about their own fluctuating mood states, as one clinically-depressed fifteen year old, with a history of chronic trauma put it: "It's not really easy to make sense of cos [sic] when you're in that mood, you don't think of anything like you don't think logically, but then like once you've sort of calmed down and everything, I sort of sit and think 'Why was I like that?'[...] And it doesn't really make sense". Albeit in a relatively small sample, a prospective longitudinal neuroimaging study observed developmental acceleration of the “hot” system’s amygdala, but only in adolescent females with depressions relative to control adolescents<sup>7</sup>. Notably, adolescent males with depressions showed developmental attenuation of the amygdala<sup>7</sup>. This suggests that pathways to depressions in adolescence may be sex-specific.

Might attenuated development of the “cold” system also generate an exaggerated imbalance between “hot” and “cold” systems thereby conferring risk for psychopathological outcome? Hippocampal reductions have indeed been observed in women with depression and a history of abuse in childhood relative either to women with depression and no history of childhood abuse or to healthy women<sup>24</sup>. Results in adolescents with depression is less clear, with cross-sectional studies showing both significant reductions and no significant differences in hippocampal volumes relative to healthy controls<sup>25,26</sup>. Some posit that the delayed developmental trajectory of the hippocampus relative to the amygdala hinders the detection of hippocampal volumetric changes until adulthood<sup>23</sup>. Longitudinal studies account for variance both within and across

individuals and so are better suited than cross-sectional studies, which only examine variance across individuals, for detecting differences in the developmental trajectories of brain regions such as the hippocampus during adolescence. Others have speculated that exposure to environmental stressors may initially potentiate but with increasing chronicity or severity eventually attenuate development of the “cold” system in some individuals, leading to reduced neural connectivity between regions and protracted overall growth<sup>18</sup>. This view is harmonious with the suggestion that dysfunctional “cold” cognitive processes precede depressive illness<sup>19,21</sup> and with prospective longitudinal data associating attenuated hippocampal growth in adolescence with developing depression in both male and female adolescents<sup>7</sup>.

Attenuated development of the “cold” system is compatible with the glucocorticoid vulnerability hypothesis, which holds that chronic stress negatively interferes with our ability to withstand and overcome trauma-related neuropathology<sup>27</sup>. Indeed, some researchers propose that brain structural and functional malleability (i.e., neuroplasticity) is perturbed by chronic stress or stress dysregulation, contributing to the emergence of depressions<sup>28</sup>. Antidepressant treatment inhibits and sometimes reverses neuroplastic damage, particularly in the hippocampus<sup>28</sup>. The hippocampus, a core region of the “cold” system, is particularly susceptible to atrophy, perhaps resulting from the previously mentioned epigenetic effects on BDNF<sup>10</sup> or, given the abundance of glucocorticoid (cortisol in humans) receptors in the hippocampus, from toxic levels of corticoids circulating in the brain (i.e., acquired neuroendangerment)<sup>21</sup>. Rodent studies show that stress can down-regulate glucocorticoid receptors in the hippocampus, leading to an overabundance of glucocorticoids<sup>27</sup>. The hippocampus typically exerts an inhibitory effect on the stress response. In conditions of chronic stress, however, the inhibitory response by the hippocampus is impaired<sup>27</sup>. In line with these studies in rodents, high levels of both evening cortisol and symptoms of posttraumatic stress disorder have been related to volumetric reductions in the hippocampus of children with a history of maltreatment<sup>29</sup>. Immediate and long-term effects of cortisol hypersecretion on the

hippocampus likely depends on the developmental stage of the hippocampus at the time of stress exposure<sup>23,29-30</sup>, the amount and chronicity of cortisol release induced by the stressor<sup>23,29</sup>, and the severity and chronicity of stress exposure<sup>23,29</sup>. Accordingly, an epidemiological study observed a four-fold increase in risk for childhood memory impairments in adults who had been exposed to four or more adverse experiences in childhood or adolescence<sup>31</sup>. By contrast, acute stress experienced in adulthood may lead to reparable hippocampal damage<sup>27</sup>. Aberrant hippocampal function could contribute to impaired concentration, anhedonia or stress dysregulation via connectivity with the dorsolateral prefrontal cortex, nucleus accumbens, and hypothalamus<sup>28</sup>. Individuals with depression, therefore, may be more susceptible to corticoid-mediated acquired neuroendangerment of the hippocampus, which could have downstream effects on experience-dependent learning<sup>21</sup>. Hence, depressive episodes could emerge in vulnerable adolescents when proximal stressful life events occur and trigger depressive symptoms<sup>21</sup>. A recent study ~~(Midgley et al., under review)~~<sup>32</sup> demonstrates the way in which many clinically depressed adolescents link the occurrence of depressive episodes to stressful life events, leaving them unable to use the reflective 'cold' system to regulate the hyper-activation of 'hot' systems. As one severely depressed 16-year old girl, who had been exposed to severe domestic violence between her parents, explained: "There's loads and loads of things that are flying around in my head and I can't stop them and look at them and find out what exactly it is and what caused them, I just know that like when it happens it makes you feel sick and dizzy and just horrible".

To summarize, synthesis between existing theories is required in order to provide a sufficient neurodevelopmental theoretical framework with which to explain adolescent onsets of mental illness including clinical depressions. Intervention at these earliest stages of illness onset may be important in preventing the neural and cognitive scars fuelling recurrence risks through into adult life<sup>33</sup>. To assist in the early detection and treatment of depression clinicians working with parents, who themselves may be mentally unwell, could better educate their patients about the environmental and physical risk

factors associated with developing MDD, the symptoms of MDD in adolescence, and facilitate discussions to improve parent-child communication and interaction. Adolescents with MDD and a positive family history of MDD could be treated with DNA demethylases or histone deacetylase inhibitors in an effort to assuage epigenetic and genetic manifestations of the disorder<sup>34</sup>. Furthermore, public health campaigns and educational establishments could ensure exposure of all children to enriched educational environments, assist in educating the general public (including adolescents) about the symptoms associated with MDD in adolescence, and disseminate knowledge about the risks associated with early sexual maturation and development. Finally, in addition to the therapeutic treatment of adolescents, training interventions focused on instilling positive biases, regulating stress and improving executive function skills could be developed and applied in supplement to any necessary pharmacological treatment, in an effort to cultivate the growth of cold system regions in an effort to redress the balance with the hot system<sup>19</sup>. As the parent of one depressed adolescent put it, after a short-term therapeutic intervention, which focused on helping adolescents to develop greater balance between the reflective 'cold' and the reactive 'hot' processing systems: "He's certainly not in the dark place where he was... he can now say 'this is upsetting me' or 'that makes me angry' – he's now able to analyse some of his feelings".

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