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Critical periods for the neurodevelopmental processes of externalizing and internalizing

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Abstract

Research on neurobiological development is providing insight into the nature and mechanisms of human neural plasticity. These mechanisms appear to support two different forms of developmental learning. One form of learning could be described as *externalizing*, in which neural representations are highly responsive to environmental influences, as the child typically operates under a mode of hedonic approach. A second form of learning supports *internalizing*, in which motive control separates attention and self-regulation from the immediate influences of the context, particularly when the child faces conditions of avoidance and threat. The dorsal cortical networks of externalizing are organized around dorsal limbic (cingulate, septal, lateral hypothalamic, hippocampal, and ventral striatal) circuits. In contrast, the ventral cortical networks of internalizing are organized around ventral limbic (anterior temporal and orbital cortex, extended amygdala, dorsal striatal, and mediodorsal thalamic) circuits. These dual divisions of the limbic system in turn self-regulate their arousal levels through different brain stem and forebrain neuromodulator projection systems, with dorsal corticolimbic networks regulated strongly by locus coeruleus norepinephrine and brain stem raphe nucleus serotonin projection systems, and ventral corticolimbic networks regulated by ventral tegmental dopamine and forebrain acetylcholine projections. Because the arousal control systems appear to regulate specific properties of neural plasticity in development, an analysis of these systems explains differences between externalizing and internalizing at multiple levels of neural and psychological self-regulation. In neuroscience, the concept of critical periods has been applied to times when experience is essential for the maturation of sensory systems. In a more general neuropsychological analysis, certain periods of the child's development require successful self-regulation through the differential capacities for externalizing and internalizing.

The embryonic brain is organized in large part through mechanisms of gene expression that guide neuronal migration to form the large-scale architecture of neural networks (Rakic, 2009). In this process, human neuroembryogenesis recapitulates the broad outlines of the vertebrate neural plan, providing the student of neuroembryology with important evidence on the architecture of human neural systems as they are organized from both pallial (primitive cortex) and subpallial (primitive basal ganglia) origins (Tucker & Luu, 2012). Once neurons reach their target locations, network organization proceeds through self-regulation by epigenetic mechanisms mediated by interactions with other neurons, including activity-dependent synaptic maintenance (Marin-Padilla, 1998). In addition to the traditional model of genetic control of biological development, it has become clear that epigenetic mechanisms not only regulate gene expression but also are essential for a systems-level self-organization of the developmental process (Gottlieb & Willoughby, 2006; Waddington, 1942).

At birth, epigenetic mechanisms become highly responsive to environmental influences (Sweatt, 2013). In studies of rats and mice, these environmental influences include not only interpersonal stress but also maternal support, such as licking and grooming (Day & Sweatt, 2011). As a result, there is renewed interest in understanding human epigenetic mechanisms that mediate the influence of social support on neural development (Day & Sweatt, 2012). Neuroscience research has identified critical periods during which the plasticity of neural networks leads environmental stimulation to be highly influential (Hubel & Wiesel, 1965). Although this research has focused on the stages of plasticity in sensory systems, there is also evidence that human development involves an extended period of plasticity of the limbic cortex, even as sensory and motor cortices become stable and mature (Barbas, 1995, 2000). The effect of this extended limbic plasticity is to provide the human child and adolescent with an extended neoteny that provides not only flexibility but also vulnerability in both motivation and memory consolidation mediated by limbic systems (Barbas, 1995, 2000; Cicchetti & Tucker, 1994).

Examining both the cortical networks and the subcortical circuitry of the human cerebral hemispheres suggests that there is not one limbic system but two (Tucker & Luu, 2006). The dorsal limbic system centered on the hippocampus and cingulate cortex includes a subcortical circuitry involving the anterior nuclei of the thalamus, the medial septum, and the medial hypothalamus (Tucker & Luu, 2007). This limbic division is interconnected with the dorsal cortex of the cerebral hemispheres, which has a unique (pyramidal cell dominant)

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neuronal network architecture and a unique (matrix projection) form of thalamic control (Tucker & Luu, 2012). With strong modulation by the locus coeruleus norepinephrine neuromodulator system, the dorsal corticolimbic division appears particularly important to orienting attention to the external context, a control mode we describe as *externalizing*.

The ventral limbic system, centered on the amygdala, the piriform cortex, and the insula, includes subcortical circuitry involving the mediodorsal nucleus of the thalamus, as well as the striatal–pallidal circuits important to both cognition and motor control. This limbic division is interconnected with the ventral cortex of the hemisphere, with a unique (granular cell dominant) cytoarchitectonics and a unique (core projection to Layer 4) form of thalamic control (Tucker & Luu, 2012). With strong modulation by the nucleus basalis cholinergic projections and the ventral tegmental area dopamine projections, the ventral corticolimbic division appears important to focusing attention particularly under aversive challenges, a control mode we describe as *internalizing*.

In considering the importance of neural plasticity for developmental psychopathology, it is important to consider not only critical periods in the maturation of sensory and motor systems but also what may be critical periods for the externalizing and internalizing functions of these dual limbic systems. In the present paper, we begin by outlining concepts of neural plasticity and critical periods. We emphasize not only the responsiveness of neural networks to influence from experience but also the mechanisms of homeostatic plasticity that maintain the capacity of neural networks to organize themselves coherently.

In considering the evidence on the processes of neural development, we point to the evidence that successful development requires not only open periods of plasticity but also mechanisms for maturation of neural systems that involve closing plasticity and instantiating stable modes of network function to insure stable modes of behavioral function.

Perhaps the most important realization is that the neurodevelopmental process begun in embryogenesis continues in postnatal ontogenesis through the mechanisms of activity-dependent specification of synpaptic plasticity in the normal processes of behavioral learning. We review evidence that mammalian learning involves differential contributions of the dual limbic systems, with the dorsal division providing a mode of externalizing that organizes a holistic model of the adaptive context. In a complementary fashion, the ventral division provides a mode of internalizing, with a focused response to events that are discrepant with this context model.

We then review the manifestations of these neurodevelopmental processes at the psychological level, reviewing the research on child psychopathology that points to patterns of disordered self-control described as externalizing or internalizing. We propose that in normal ontogenesis, what are essentially neurodevelopmental mechanisms of internalizing and externalizing function as adaptive modes of normal self-regulation. In important ways, the mode of externalizing is the child's fundamental basis for learning in the early years. It is increasingly balanced by internalizing as plasticity becomes restricted and as coping becomes more focused on mature behavioral and cognitive function.

This theoretical account of self-regulation of the neurodevelopmental process builds from concepts of neuromodulator control of neural plasticity in embryogenesis to explain multiple levels of neural function during behavioral development, including arousal, mood, and the motive biases regulating learning. Each of these levels of neural function can be seen to shape both normal and abnormal modes of psychological self-regulation in the process of social development. By understanding the nature of neural plasticity at these multiple functional levels of brain organization, we may find new ways of thinking about critical periods in the development of psychopathology.

Critical Periods in Developmental Self-Regulation

A fundamental insight is that the epigenetic regulation of neural development, through the mechanisms of neural plasticity, is continuous throughout life. In the embryonic development of the mammalian brain, activity-dependent plasticity organizes the fine pattern of neuronal connections that has been framed only in general outline by genetic control of trophic factors. After birth, neural plasticity then remains integral to the processes of learning and memory as these processes continue to shape the fine architecture of cerebral networks (von de Malsburg & Singer, 1988). After the abundant formation of synapses among neurons in embryonic and early infant development, the maintenance of synaptic connections is maintained by use-dependent activity (Greenough & Black, 1992). In determining this activity, the regulation of the arousal level of the brain becomes a key theoretical issue for understanding both emotional development and neural development (Trevarthen, 1984, 1986). Motive arousal and the self-regulation of neural activity can be recognized shaping both psychological function and neural development. The separation of psychological and biological levels of analysis may remain a limitation of today's scientific disciplines, but it is no longer interesting for scientific theory. Cognition is neural development, continued in the present moment (Tucker & Luu, 2012).

Even though it is thus ongoing, and cumulative, neural development does progress through critical periods. At critical points in development, the architecture of neuronal assemblies depends not only on internal regulatory coherence but also on effective contact with environmental information. In classical neuroscience research, the emergence of a critical period in development reflects an opportunity for understanding how neural plasticity arises, such as when environmental input is required to allow maturation of a sensory system (Hubel & Wiesel, 1965). Recent evidence suggests that critical periods for adapting to environmental information are opened when homeostatic neural mechanisms, such as the maturation of inhibitory control, shift the brain from a dominance of internal control to a new responsivity to external information (Hensch, 2005a). In the development of the mammalian visual system, for example, effective binocular vision, supported by ocular dominance columns of the cortex, emerges

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only if the maturation of inhibitory control suppresses the ongoing (internal) oscillatory activity to allow visual cortical neurons to respond to visual input (Toyoizumi et al., 2013). The essential complement to the opening of a critical period is the close. We must understand how the neural system becomes less responsive to environmental input, as the process of increasing maturation stabilizes the system to allow effective perceptual, cognitive, and behavioral function.

Opening and closing windows in neural development

The identification of critical periods in brain development has come from research on the necessary role of environmental experience in the healthy maturation of sensory systems, such as the visual system (Hensch, 2005b). Whereas certain aspects of the maturing neural function are specific to the sensory system, such as the formation of ocular dominance columns, other aspects, such as the need for establishing the appropriate balance of excitatory and inhibitory input, may reflect more general self-regulatory mechanisms for neural development.

As outlined above, activity-dependent specification of neural connections is an integral component to the growth and differentiation of neural networks. Although it may seem as if visual experience simply exercises the relevant neural networks to allow this use-dependent connectivity to take form, the control of inhibitory as well as excitatory balance is integral to this developmental process (Takesian & Hensch, 2013). Understanding the process of opening and closing a critical period in the visual system may be important to appreciating the brain's self-regulation of neural activity in general terms, including global controls on arousal and inhibitory tone.

For example, the maturation of inhibitory capacity in the visual system appears to open a critical window for neural plasticity, as seen in the establishment of ocular dominance columns through visual experience (Toyoizumi et al., 2013). Accelerating the function of GABAergic inhibitory control, such as with administration of benzodiazepines, accelerates the opening of the critical period for establishing ocular dominance (Hensch, 2005b). A specific class of GABAergic inhibitory interneurons, the fast-spiking interneurons with parvalbumin channels, is responsible for this critical regulatory effect of neural inhibition; enhancing the activity of other GABA interneurons does not have this effect (Takesian & Hensch, 2013).

It may seem paradoxical that an inhibitory control is responsible for opening the critical period for sensory input to condition the architecture (dominance columns) of the visual cortex. However, this effect illustrates the importance of neural activity controls, specifically those that balance excitatory and inhibitory processes within the key processing networks of the cortex and its subcortical (thalamic, cerebellar, striatal, limbic, and midbrain) control systems (Hensch, 2005b). The regulation of developing cerebral networks involves various modes of oscillatory synchronization, beginning in the embryo and continuing throughout development (Takesian & Hensch, 2013). In considering such mechanisms, Toyoizumi et al. provide a theoretical analysis in which the primary effect of maturation of inhibitory controls is the suppression of ongoing, "background," or internally generated oscillations, such that neural activity and synaptic alterations could be responsive to environmental input (Toyoizumi et al., 2013). In this regard, the developmental progression of the critical period shifts control from internal toward external influences to allow the brain to reflect qualities of the environment.

A number of findings thus suggest that there is a progression in the organization of critical periods in the brain, such that the transition from internal control of ongoing neural activity to responsiveness to external input progresses from initial plasticity in elementary sensory areas toward greater plasticity in association cortex and integrative networks (Toyoizumi et al., 2013). This hierarchic organization of neural plasticity may be analogous to the classical observation that myelination (and thus maturation) of cortical networks begins first in primary sensory and motor areas, and only later involves association regions, including the temporoparietal cortex and, continuing well into adolescence, the frontal cortex (Yakovlev & Lecours, 1967).

It is important that the close of a critical period appears to be due, not to a loss of the capacity for plasticity, but rather to an active "lock" on the neural architecture to insure stability of neural and cognitive function in the face of continued interaction with the changing environment (Hensch, 2005a). When these lock or braking mechanisms are removed, juvenile plasticity may be restored to a mature neural architecture (Takesian & Hensch, 2013).

It may seem as if perpetual plasticity would be an advantage for adaptive development. Human neoteny does appear to have evolved to extend the juvenile period to an unprecedented degree (Gould, 1977). However, once effective patterns of perception and behavior are achieved, it may be essential to protect the underlying neural representations from the continued interference caused by undisciplined learning. In distributed representational systems, such as the mammalian brain, computational modeling has shown that there is an inherent trade-off between plasticity and stability, known as the *stability–plasticity dilemma* (Grossberg, 1980). Because representations are distributed, all existing knowledge of the system is modified with any new learning, resulting in what is described as *catastrophic interference* of new input with existing knowledge (Hinton, Plaut, & Shalice, 1993). As a result, protecting the brain from neural plasticity is as important to successful development as enabling it.

Developing homeostatic plasticity

Whereas the regulation of neural plasticity can be seen as an active control on the learning process, there are also controls that appear to restore or reset properties of neural networks, in a homeostatic fashion (Turrigiano, 2007). From examining these homeostatic controls, researchers have concluded that the ongoing plasticity of daily learning has a cost to the engaged networks, and a compensatory or homeostatic rework

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of network connections is required to allow the brain to restore its networks to be receptive to the next learning experiences (Turrigiano, 2012). To the extent that the modulation of synaptic connectivity in neural plasticity induces costs for the network, it would seem that the regulation of critical periods in development must engage parallel processes of regulating homeostatic plasticity.

The most striking example of homeostatic regulation of neural plasticity may be sleep. Specific neurophysiological mechanisms, including cortical slow oscillations and abrupt shifts in neuromodulator controls in REM sleep, achieve what appear to be essential homeostatic changes in neural networks that allow continued adaptive plasticity in waking experience (Cirelli & Tononi, 2008; Tononi & Cirelli, 2006). Because these ongoing diurnal mechanisms of cerebral networks appear to be essential to memory consolidation, the biological analysis of learning in development must consider not only discrete changes in learning experiences but also the ongoing process of homeostatic adaptation that sets the stage for those discrete forms of plasticity in learning. Disruptions of sleep may be expected to have rapid, profound, and not always reversible effects on the neurodevelopmental process, and thus the emergence of psychopathology.

Traumatic experiences as critical periods?

For the maturation of sensory systems, it is reasonable to consider the developmental period for certain forms of plasticity, such as forming ocular dominance columns, as opening and then closing. However, research on plasticity in developing neural systems shows that the engagement of strong neuromodulator influences, such as acetylcholine projections from the nucleus basalis, in strong motive states may induce a high degree of neural plasticity outside of the traditional critical period window (Carcea & Froemke, 2013). As we develop the theoretical model of this paper, we will consider the processes of externalizing and internalizing as engaging important periods of plasticity at certain pivotal learning periods in the child's development. However, it may be important to note from the outset that, in addition to the adaptive regulation of development through the learning controls of internalizing and externalizing, there may be unusual processes of neural plasticity engaged by the strong emotional states (and neuromodulator engagement) of traumatic experiences. Certain primitive responses, such as freezing, may be engaged in a traumatic experience, with an unusual quality of learning that is not well integrated with ongoing neuropsychological development (Baldwin, 2013). In such examples, traumatic experiences may engage exaggerated forms of neural plasticity that themselves may present critical periods in the neurodevelopmental process.

The isomorphism of motive states and neurodevelopmental controls

Although neuroscientists have studied critical periods in development primarily in relation to the neural plasticity in sensory systems, the influences of strong motive states may need to be understood more generally. The disorders of development in psychopathology do not involve discrete sensory deficits, but rather more general problems of motivational, emotional, and social self-regulation that affect the entire organism. In classical neurodevelopmental studies, such as of the maturation of myelination (Yakovlev & Lecours, 1967), the sensory (and motor) areas show relatively early maturation (and loss of plasticity), compared to more integrative areas of the association cortex, which remain plastic. Particularly for frontal areas, these integrative regions of cortex continue to show signs of myelination (and thus slow and continuing maturation) well into adolescence.

As the neuroscience methods for characterizing neural plasticity and maturation have become more sophisticated in recent years, the evidence continues to suggest that sensory and motor areas of the cortex mature, and lose plasticity, early, whereas association cortex and specifically limbic cortex may retain a high degree of plasticity into adulthood (Barbas, 1995). In reviewing this evidence, Barbas suggests that one effect of continued neural plasticity in limbic cortex and associated subcortical circuits may be the continued flexibility in learning and memory throughout the long human childhood. At the same time, Barbas suggests that this extended flexibility of the human juvenile period may present the risk for vulnerability to both neurological and psychiatric developmental disorders (Barbas, 1995).

The extended plasticity of limbic networks may be particularly important through continuing immaturity of the limbic control of the brain stem, midbrain, and forebrain neuromodulator systems that regulate the brain's activity level. In a general sense, the activity-dependent plasticity regulating the child's differentiation of cerebral architecture in the process of neuropsychological development is dependent on neural activity. The brain stem and midbrain neuromodulators, including serotonin, dopamine, norepinephrine, and acetylcholine, regulate the activity of widespread limbic, striatal, and cortical networks, including the balance between excitatory and inhibitory influences that is critical to critical periods (Takesian & Hensch, 2013). The forebrain nucleus basalis cholinergic projections appear particularly important to regulating the state of activity in human cortical and thalamic networks that determines developmental plasticity (Takesian & Hensch, 2013).

In addition to setting the tone of neural activity that is essential to learning, the qualitative changes in ongoing neural activity that are controlled by these neuromodulator systems may be essential to the homeostatic plasticity that is required for healthy and effective function of the child's cerebral networks. For example, in sleep, there are large cortical slow oscillations in neural activity that seem to provide some homeostatic restorative function to normalize the synaptic weights that have been conditioned by the experience of the day (Tononi & Cirelli, 2006). The consolidation of memory for normal learning appears to be strongly dependent on slow wave sleep (Tononi & Cirelli, 2006). The child's developing ability to self-regulate behavior, experience, and neural organization

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would seem to be dependent on adequate motivational tuning of cerebral arousal in waking activity, as well as on the homeostatic mechanisms of plasticity in sleep. Sleep disorders may then represent pernicious sources of developmental psychopathology (Benca, 1996).

Understanding the specific developmental influences of neuromodulator systems may be one of the most important challenges for gaining theoretical insight into developmental psychopathology. The regulation of neural development by the neuromodulator systems begins in embryogenesis, where norepinephrine, for example, is essential for establishing connections of pyramidal cells as they migrate to superficial layers of the cortical sheet (Marin-Padilla, 1998). Acetylcholine, controlled from the forebrain nucleus basalis, appears to be essential to the embryological organization of the subplate region of the incipient cortex (Hanganu-Opatz, 2010). At birth, the neuromodulator pathways continue to function as developmental control systems, regulating the child's neural activity in ways that are fundamental to neural plasticity, for example, in the operation of critical periods. Whereas the auditory cortex of juvenile animals reorganizes its tonotopic map in response to auditory input, this ceases to occur in adult animals, indicating the close of the critical period (Takesian & Hensch, 2013). The exception occurs if there is strong cholinergic (acetylcholine) input from the nucleus basalis (Takesian & Hensch, 2013). The arousing or modulatory influence of the forebrain cholinergic control system thus directly alters the plasticity state of auditory cortex, and its modifiability by experience.

In a similar fashion, it seems likely that motivational control of the child's brain function, mediated through specific neuromodulator control systems, continually tunes the state of neural plasticity in response to environmental challenges, in ways that must be appropriate to the general task of self-organization at each developmental stage. Although the neuromodulator systems may often represent the final common path in controlling plasticity in learning, and in the modes of homeostatic plasticity in memory consolidation and sleep, the control of the neuromodulator systems must be understood through a more general theoretical model of the brain's vertical organization of telencephalic, diencephalic, mesencephalic, and brain stem systems (Tucker, 2007). Consistent with the pivotal role of limbic plasticity in human development (Barbas, 1995), some of the most important outputs of limbic controls are to the subcortical circuits that regulate the brain stem neuromodulator systems (Pribram, 1981). Whereas the notion of the limbic system has been one of the most difficult concepts in neuroscience, it remains an essential concept for relating key functions of the cerebral hemispheres (memory consolidation and motivational control) to the subcortical circuitry (striatal, hypothalamic, thalamic, and midbrain). The limbic system and its subcortical circuitry form the fundamental basis for the brain's self-control (Heimer, Van Hoesen, Trimble, & Zahm, 2007).

Certain critical periods in neuropsychological development may present particular vulnerability for the development of psychopathology. Beginning with the classical recognition of the control of embryonic morphogenesis by the major neuromodulator systems (Trevarthen, 1986), we consider the isomorphism of neuromodulator control of motive states in behavior with the neuromodulator control of neural development generally (Tucker & Luu, 2012). We attempt to formulate concepts of neural plasticity at the organismic level, where periods of externalizing or internalizing influence experience, behavior, and neural development broadly. This organismic approach may be likened to the concept of probabilistic epigenesis (Gottlieb & Willoughby, 2006), wherein epigenetic mechanisms are not limited to the molecular processes that regulate gene expression but are more general self-regulatory controls that build from the development base of phenotypic gene expression to mediate the child's continuing process of self-organization in the social context. At a basic level, the epigenetic mechanisms involve the interactions among neural systems that achieve functional neural architectures that are only approximately specified by gene expression. At a more complex system level, epigenetic mechanisms involve the child's psychological capacities that organize cerebral resources in ways that articulate the process of developing intelligence.

Cognition and neural development

The theoretical perspective we adopt is one in which neural development and psychological development are understood to be identical (Tucker & Luu, 2012). Cognition is neural development, continued in the present moment.

In the process of neural development, specific forms of neuromodulation appear to alter ongoing neural activity in specific ways that not only shape the quality of learning but also shift the child's attentional focus between external and internal orientations. These orientations may help explain the manifestations of child behavior problems that have been described as *externalizing*, in contrast to those described as *internalizing*.

Whereas social and motivational factors are now widely recognized to influence the epigenetic control of neural development (Liu et al., 1997), it is not straightforward to understand the implications for human development. For rat pups, licking and grooming appear to be essential supports for early brain development. For human children, the need for physical contact and social support may not be that different at a basic level, yet there are more complex challenges of adaptation to the interpersonal and educational environment that involve psychological capacities of self-organization.

At the psychological level, the control of neural activity involves states of emotional arousal and motivational readiness. There is an important specificity to the control of neural arousal, with certain neuromodulator systems supporting a positive hedonic state, approach motives, and engagement of external contacts, and other systems associated with anxiety, hostility, and the avoidance of environmental interactions. We review the evidence that the differing motive biases

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of these neuromodulator systems are integrated with fundamentally different modes of learning and memory consolidation, such that the self-regulation of the child's learning process proceeds differently depending on the dominant motive state. There appear to be dual motive control systems that bias the child's neural and psychological orientation toward external engagement, on the one hand, or toward internal focus and disengagement, on the other hand. As a result, a theoretical model of these neural control systems may present opportunities for understanding how the process of neural development may lead to sensitive periods in the formation of lifelong patterns of psychological function and dysfunction that have been described classically as internalizing and externalizing disorders (Achenbach, 1982).

We begin with an overview of the concepts of internalizing and externalizing symptom patterns in developmental psychopathology, with an emphasis on both the cognitive process and the subjective experience associated with these disorders in classical psychological theory. We then consider evidence that the motivational controls on learning differ in two divisions of the limbic system in ways that may explain the bias toward internalizing or externalizing. The dorsal division of the limbic system, involving the cingulate cortex, hippocampus, and septal–hypothalamic circuits, may bias learning toward externalizing, particularly when conditions favor approaching a familiar and predictable context (Tucker & Luu, 2012). The ventral division of the limbic system, centered on the amygdala, piriform cortex, and orbital frontal lobe, may bias learning toward internalizing, particularly under conditions of threat or unpredictability (Tucker & Luu, 2012).

We then consider the specific neuromodulator controls, involving the basal forebrain, hypothalamus, and midbrain, that regulate both neural arousal and affective state differentially for these dual divisions of the limbic system. The modes of internalizing and externalizing cannot be reduced to these neuromodulator control systems, of course, and must be understood in relation to the multiple levels of neural circuitry regulating the limbic control (through dual limbic systems) of the learning process. Nonetheless, in a simplistic but hopefully illustrative theoretical model, we assert that the dual learning modes of the dorsal and ventral limbic systems involve fundamentally opposite biases for engaging the environment, including the child's interpersonal relations, in ways that could be described as biases toward introversion or extraversion. At the same time, these limbic modes engage specific neuromodulator controls on neural activity that are not only integral to familiar affective states (elation, depression, anxiety, and hostility) but also apply specific regulatory influences of habituation and sensitization on the process of neural plasticity in learning and thus the process of neural development.

Because these neuromodulator arousal controls serve to engage the immediate processes of learning and memory, they can be said to relate to the active plasticity of learning rather than the background or homeostatic plasticity. Nonetheless, the major neuromodulator controls appear to bias the general temporal dynamics of cerebral networks in general ways. One bias is toward rapid habituation of activity (norepinephrine); another bias is toward sensitization or increasing redundancy of ongoing activity (dopamine). We suggest these modes of network bias could be described as *allostatic* forms of neural plasticity, meaning that the state of the network becomes biased in a particular direction of synaptic activity with a specific functional goal in network connectivity that is consistent with a certain bias in the motivational control of learning. Whereas homeostasis brings the system toward a state of balance, allostasis biases it in an unbalanced mode (habituation or sensitization) that prepares for a certain mode of adaptive function. The motive states of elation and anxiety reflect these adaptive bias modes, tuning attention and working memory in general ways that shape the more discrete sensory and motor operations.

We thus outline a theory of dual modes of allostatic plasticity for the dorsal and ventral divisions of the limbic system that can explain important aspects of internalizing and externalizing, in both normal and abnormal development. These have been considered as processes of psychological self-regulation, but they also may be processes of neurodevelopmental self-regulation, shaping the ongoing synaptic differentiation of the child's neural architecture. We then consider critical periods of development in which the bias toward internalizing or externalizing may be established in ways that may be enduring for either normal or abnormal patterns of neural development.

Externalizing and Internalizing in Personality and Psychopathology

To go beyond diffuse notions of environmental insults causing developmental disorders, it is important to explain the specific developmental trajectories that lead to human psychopathological outcomes. A conventional approach would be to undertake an analysis of each diagnostic syndrome, such as for affective disorders or schizophrenia, and to consider how neural plasticity could be involved in the neural disorder underlying that syndrome. An alternative approach, consistent with the recent emphasis on research domain criteria for adaptive functioning (Cuthbert, 2014), is a dimensional analysis. Classical descriptive studies of child behavior problems have suggested there are basic dimensions of the child's self-regulation that, when challenged in the course of development, lead to predictable psychopathological outcomes.

Dimensions of child experience and behavior

The classical factor analytic studies of child behavior problems by Achenbach (1982) revealed that a higher order dimension of *internalizing* versus *externalizing* could describe the clustering of specific behavior problems across children. Externalizing disorders such as attention-deficit/hyperactivity disorder and conduct disorder involve behavior patterns of "acting out," or impulsivity, with insufficient self-regulatory

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constraint over behavior. Internalizing disorders such as anxiety, depression, or obsessive–compulsive disorder involve more personal rather than public distress, and if anything, involve excessive constraint. Even though there are important qualitative developmental changes in the psychopathology that appear in adolescence and young adulthood, such as the onset of florid schizophrenic psychosis, the personality disorders of adulthood can be seen to reflect the crystallized forms of internalizing and externalizing patterns that are first seen in the symptom clusters in child psychopathology.

Although it is possible to consider this internalizing–externalizing dimension of psychopathology in terms of appearance, that is, how the child's behavior appears to parents, teachers, and psychologists, the dimension may also capture the essential features of the child's neuropsychological self-regulation. By considering disordered behavior in relation to the psychological theory of normal development, we can interpret externalizing as a mode of self-regulation in which the child's cognition and motivation rely on vigorous contact with the environment. In contrast, internalizing is a mode in which self-regulation involves greater internal control. In Jung's original formulation, the normal personality develops through one mode of *extraversion*, where the mind is reliant on external sources for its contents (Jung 1921/1971). This is balanced by the mode of *introversion*, where the individual's mental process is more internally generated. Many of the behavior patterns thought to differentiate extraverts from introverts in adult personality theory can be seen to align with the child behavior problems differentiating externalizing from internalizing disorders (Eysenck, 1973).

Introversion and extraversion in personality

Modern personality research has involved greater emphasis on psychometric methods, rather than general theories of personality (DeYoung, 2013; Saucier & Goldberg, 1998). Yet the dimensions of introversion and extraversion remain important. In recent cross-cultural studies of personality descriptors, for example, a dimension of *dynamism* has emerged that bears considerable similarity to extraversion, and a dimension of *social self-regulation* (Saucier et al., 2013) can be seen to align with traditional dimensions of introversion or constraint.

Similarly, the Big Five dimensions of personality can be seen to cluster in two higher order dimensions (described by DeYoung as *stability* and *plasticity*) that involve strong loadings of neuroticism or introversion (stability) and extraversion (plasticity; DeYoung, in press). Tellegen's (1985) factor analytic studies of both emotion and personality have revealed similar dimensions of positive emotionality (extraversion) and negative emotionality (introversion).

In a developmental analysis, therefore, it may be possible to interpret the childhood disorders of externalizing and internalizing as exaggerations or disruptions of what may be normal patterns of self-regulation. Theoretical models of temperament and self-regulation, including those that have considered explanations in terms of neural systems, have emphasized the continuity of psychopathological disorders with the efforts of normal children to achieve effective self-organization of behavior (Cicchetti & Tucker, 1994; Derryberry & Rothbart, 1984; Derryberry & Tucker, 2006).

Internalizing and externalizing as modes of cognitive control

These modern approaches to self-regulation and cognitive control have developed themes that were initially formulated in the ego psychology movement of psychoanalytic theory in the context of psychotherapy (Pribram & Gill, 1976; Tucker & Luu, 1998). Classical psychological analyses of adult personality disorders, based on extensive studies of psychological tests as well as therapeutic interviews (Rapaport, 1948; Shapiro, 1965), emphasized characteristic patterns of cognitive control that were associated with lifelong behavioral patterns of externalizing and internalizing. Although these studies primarily involved clinical assessment with adults, the theoretical analysis often described the cognitive patterns as resulting from developmental roots in childhood and adolescence, including biases toward externalizing or internalizing as developmental patterns of self-regulation.

In histrionic (hysteric), psychopathic, and impulsive disorders, the pattern of externalizing behavior is associated with cognition that is clearly extraverted. The person's thinking is highly reactive to immediate environmental influences, or to immediate personal urges, with minimal capacity for either deliberate analytic thought or constraint of impulses (Shapiro, 1965). The characteristic affective orientation is inappropriately positive in relation to environmental circumstances described as "la belle indifference."

In contrast, with internalizing personality disorders, including obsessive–compulsive and paranoid personalities, an opposite pattern of cognitive self-regulation is observed, a pattern that could be described as pathological introversion. The person's thinking is highly controlled and deliberate, with behavior and cognition constrained to an inordinate degree. The negative affective tone infuses attention, leading to expectancy for threats and a vigilant apprehension for danger (Shapiro, 1965, 1981).

A dimension of self-regulation varying from extraversion to introversion can thus be deduced from several lines of evidence, including the patterning of child behavior disorders, the covariance of normal emotional states and personality traits, and the characteristic psychological processes observed in personality disorders. The theoretical implication for neuropsychological development is that fundamental modes of self-regulation involve both the child's internal psychological controls and the characteristic orientation toward the social environment, with this orientation varying from strong external engagement to strong avoidance and strivings for autonomy.

It may seem as if the impulsive or extraverted personality reflects a lack of self-regulation, rather than a specific style or mode of self-regulation. Yet it is important to move beyond

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conventional cultural notions of self-control and to consider the neurocybernetics or neural control systems in the developmental process. In this scientific analysis, the mode of externalization and impulsive action must be recognized to be a self-regulatory device that is fully as important as the mode of internalization, restriction of behavior, and cognitive and emotional constraint (Tucker, 2007; Tucker & Luu, 1998).

In a psychological analysis, then, the themes of internalizing and externalizing are fundamental modes of cognitive control, reflecting how coherent systems of motive self-regulation shape the ongoing cognitive process. The original work on cognitive controls was formulated in relation to psychoanalytic notions of libidinal motivation, ego controls, and defense mechanisms, notions with dubious theoretical capability and that are no longer influential in cognitive psychological theory. Nonetheless, the literature on cognitive controls has provided a solid basis in descriptive evidence, such as in the analysis of psychological test results (Rapaport, 1948; Shapiro, 1965), that remains relevant to modern concepts of temperament, self-regulation, and effortful self-control (Derryberry & Rothbart, 1988, 1997). Building from both the traditional and the recent theoretical formulations, we can frame the question for a biological analysis of neural plasticity: how to understand systems of neural control that organize major trajectories in the brain's developmental plasticity (Waddington, 1942) that can explain these characteristic themes of psychological self-control.

Neurodevelopmental Processes of Externalizing and Internalizing

The organization of the vertebrate nervous system can be seen to include qualitatively specific ways for controlling neural activity that differ for sensory processing versus motor processing. In studying these control methods, they seem to involve continuity across multiple levels of neural function, from synaptic regulation in neural networks, to qualitative forms of neural arousal, to elementary learning strategies, as well as ways of structuring the child's concepts in time (Cicchetti & Tucker, 1994). To capture the continuity across these levels of analysis, we describe these control modes as *neurodevelopmental processes.* They emerge from the elementary effects of midbrain neuromodulator systems that do not simply increase the quantity of neural activity, but instead change its quality in specific, motivationally significant ways. These qualitative controls shape the process of neural development, and simultaneously motivate attention and memory consolidation, and therefore the child's experience and behavior, in general.

The primary function in the evolution of neurodevelopmental controls may have been the different requirements of the sensory and motor functions of the *somatic* nervous system. In addition, there is a similar division between the input and output (sensory and motor) functions of the *visceral* nervous system, with viscersensory and visceromotor functions regulating internal homeostatic mechanisms (Luu & Tucker, 2003b). Applying to both somatic and visceral domains, then, the motive processes of internalizing and externalizing seem to involve multiple levels of biological self-regulation, including (a) elementary brain stem and forebrain arousal systems regulating neural activity in qualitative ways, (b) limbic motive systems biasing attention toward hedonic or aversive content, and (c) dorsal and ventral corticolimbic networks organizing learning and memory in specific corticolimbic network patterns (holistic or object concepts) and in specific ways over time (by habituation or sensitization biases).

By appreciating the unique control properties of the neurodevelopmental motive processes at multiple levels of neural organization, it may be possible to understand the integral roles of neural arousal and motivational control systems in the psychological orientations of introversion and extraversion. As we have seen in the psychological analysis in the previous section, these psychological orientations appear to become exaggerated and unbalanced in the major dimensions of internalizing and externalizing disorders in psychopathology.

Neural control of extraversion: Shaping knowledge of the context

Several lines of evidence suggest there is a qualitative division of structure in cognition that parallels the functional division between the elementary motive biases in the dorsal and ventral corticolimbic systems. Perhaps ironically, given the foundations of today's cognitive neuroscience in cognitive psychology, this evidence came, not from the experimental psychology with humans that has guided modern cognitive neuroscience research, but from modern animal learning theory (Luu & Tucker, 2003b).

Beginning in the 1960s, the community of specialists in animal learning recognized that a number of well-known features of learning could be explained only if the animal's cognitive representation of expectancies for environmental events was considered (Kamin, 1968; Rescorla & Wagner, 1972; Tucker & Luu, 2007). For example, in the *successive negative contrast effect*, an animal trained to expect a high-value food, such as bran mash, quits working when a lower value food, such as sunflower seeds, is substituted. This relative devaluation of the food reward is impressive, because the lower value food is fully sufficient to reinforce behavior if it is presented initially. Rather than a passive conditioning of a biological "reinforcement" (reducing hunger) with behavior, the only logical interpretation is that the animal forms an expectancy for the higher value food. This cognitive representation, that is, this expectancy held in the animal's memory, then becomes the reference that reframes the value of the lower substitute (Tucker & Luu, 2007).

Thus, the technical analysis of animal learning proved to refute behaviorism, leading to a reformulation of the control of behavior that could only be expressed in cognitive terms. Although this transformation was not widely recognized, there were parallel discoveries in neuroscience. In research on specific cortico–limbic–diencephalic circuits of learning

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and memory consolidation in rabbits, Gabriel, Kubota, Sparenborg, Straube, and Vogt (1991) and Gabriel et al. (1983) showed that the elementary cognitive biases involved in expectant learning differed for *dorsal* limbic circuits (including the hippocampus and posterior cingulate cortex) compared to *ventral* limbic circuits (including the amygdala with input into the anterior cingulate cortex).

In these studies, the dorsal limbic networks responded only gradually to changing reward contingencies, in a kind of learning that would be described as *shaping* in traditional behaviorism. An important implication of these observations is that the animal normally maintains a *context model*, a kind of implicit, ongoing cognitive representation of self in context. This concept has a positive hedonic value, explaining effects such as the negative contrast effect. Normal learning then involves small, gradual updates to this context model (Luu & Tucker, 2003b; Tucker & Luu, 2006).

It is important to recognize that the cognition of the dorsal corticolimbic networks implied by these learning studies is, not a discrete representation of a specific sensation, or of a specific event, as might be assumed in traditional cognitive theories, but a holistic representation of the environmental context. It is not only spatial memory but also includes adaptive, visceral values of the spatial context. Furthermore, because the animal's hedonic tone and motive adaptations are integral to this context model, it could be described as a holistic representation of self in context (Tucker, 2007; Tucker & Luu, 2007). The holistic nature of the representation is fundamental; in the gradual shaping of the context model, many aspects of experience, including sensory, motor, and visceral components, appear to be consolidated into the holistic conceptual model.

By considering the nature of the animal's cognition that combines both representation of the internal state and representation of the context, the dorsal learning method can be seen as a kind of externalizing. With an integral motive basis, the hedonic model thereby situates self within the external context. The animal's cognition could be described as extraversion, in that it is dependent on the context, and only slowly changes in order to update and gradually modify that context model. Because the context is positively valued, the dominant affect is positive, biasing toward approach motivation. Because the features of the context are predicted effectively, feedforward cybernetics are appropriate, and behavior can be impulsive, actualizing current urges in ways that are congruent with the valued expectations.

Neural control of introversion: Focusing under discrepancy

In contrast to the gradual learning of the dorsal limbic networks, the ventral limbic networks appear to support what was described by Gabriel and Sparenborg (1986) as *rapid learning* when the environmental events are discrepant with the animal's expectancy. In mammalian cognition, discrepant events are typically aversive, and both continued vigilance and focused attention are necessary. The recognition of prediction discrepancy as a predictor of learning was integral to the Rescorla–Wagner model that proved effective in explaining key features of the classical conditioning literature (Rescorla & Wagner, 1972). The specificity of ventral limbic control for organizing the adaptive response to prediction discrepancies can be seen in the evidence on striatal and dopaminergic mechanisms in mediating this response (Schultz, 1998). The amygdala, anterior temporal cortex, insula, and orbital frontal regions are particularly important for the limbic representation of the striatal circuitry, closely linked to the midbrain ventral tegmental dopamine control system. Together, these limbic, striatal, and midbrain systems appear to be specialized for integrating the adaptive response to prediction discrepancies (Tucker & Luu, 2007).

This form of focused learning, mostly but not always engaged under aversive conditions (hunger or threat), can be seen as a mode of internalizing. The discrepancy of environmental events from the predictions of the context model serve to invalidate the context model, such that the animal must separate from the dorsal mode of context-embedded cognition and quickly engage a focused (anxious) anticipation of potential threat. In conditions such as hunger, the internal motive state shifts the balance toward this mode of focused attention. The integrated effect of the ventral learning method is kind of a cognitive introversion, because the adaptive bias for ongoing cognition is effected through a shift in attention separating self from the context, and thereby adopting an adversarial relation to anticipated events.

This account of learning under discrepant expectations can thus be understood in terms of modern learning theory, with unique connections to primitive motivational states (Tucker, 2007). Yet this learning mode is also inherently cognitive, in that the motive controls shift the process of attention and memory consolidation in ways that are adaptive in changing the animal's ongoing concept model for relating to the environment.

Although behaviorism explicitly denied the role of cognitive representations, even when applied to human social learning, it is interesting to recognize that some of the implications of modern animal learning theory may have been recognized implicitly in behaviorist practice. In applications both to animal learning and to clinical psychology with humans, punishment (engaging the ventral discrepancy processing system) was seen as largely disruptive and unproductive, whereas the modification of adaptive behavior was seen as best accomplished through shaping and positive reinforcement (Bandura, 1977). In the general evolutionary context for self-regulation, of course, both learning modes are essential. However, behaviorism seems to have recognized the inherent asymmetry of reward and punishment. The approach mode of learning is not symmetric with the punishment mode. Under conditions of adaptive success, the dorsal limbic mode of learning is well suited to maintaining the context model, and acquiring behavior that is effective for the context. Under conditions of threat or failure, the ventral limbic

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mode of learning disrupts externalizing and the context model and simultaneously engages vigilance and focused attention to immediate coping efforts. In this process, the internalizing mode is a disruptive and temporary one, such that fully integrated consolidation of behavioral function requires establishment of a new context model in the dorsal mode.

Regulating cognition for the spatial context or the objects of attention

Although the differentiation of dorsal and ventral limbic circuits for these modes of learning and memory consolidation may not be widely appreciated, the duality of dorsal and ventral corticolimbic networks in memory functions has been recognized, beginning several decades ago with the primate studies by Mishkin and Underleider (Mishkin, 1982; Ungerleider & Mishkin, 1982). These authors described the skill of the dorsal networks in *spatial* memory, compared to the specialization of the ventral networks in *object* memory. Mishkin (1982) differentiated the circuitry for the hippocampal base of the dorsal limbic system from that of the amygdala base of the ventral limbic regions.

The cognitive approach thus emphasizes the specialized representational qualities of the dorsal and ventral limbic networks, rather than the adaptive process involved in acquiring or changing the cognitive representations. Nevertheless, these are almost certainly different descriptions of the same underlying capacities. As the dorsal networks gradually assemble the conceptual model of the *context*, the result is a skilled representation of the spatial surround and the various perspectives of the self in that surround. When attention is more narrowly focused within the ventral networks, the resulting cognitive representation is an *object*, an adaptively significant element that is differentiated from the perceptual surround.

Dual frontolimbic methods of action regulation

The unique cognitive processes for forming concepts of contexts and objects can be explained by the cybernetic or control system properties of the dorsal and ventral limbic systems. These cybernetic properties are manifested most clearly and simply in the dorsal and ventral modes of frontolimbic control of motor processes (Goldberg, 1985; Shima & Tanji, 1998). As seen most clearly from studying the effects of lesions in humans (Goldberg, 1985; Passingham, 1987) and in single-unit recordings of neurons in monkeys (Shima & Tanji, 1998), the dorsal frontolimbic pathway (anterior cingulate to mediodorsal frontal cortex) provides a *feedforward* control of action. Movements are launched impulsively, in a manner similar to a ballistic missile (Goldberg, 1985). In contrast, the ventral frontolimbic pathway (orbital frontal to ventrolateral frontal cortex) provides *feedback* guidance of action. The feedback control of movements is regulated tightly in relation to ongoing constraint from sensory guidance, not unlike the control of a guided missile. As shown in single-unit studies of monkeys, these features appear to be characteristic of the primate frontal lobe generally (Shima & Tanji, 2000).

By considering the commonality shared by the learning processes unique to each limbic pathway and the motor control biases of that pathway, it becomes clear that there is a general and qualitative mode of controlling behavior in each of these pathways. This is what could be described as a *neurocybernetic method*. It is a method of self-regulation, based in elementary properties of feedforward or feedback control of action. The dual neurocybernetic methods of externalizing and internalizing appear to have become integrated with the unique strategies for consolidating learning and memory that have evolved within the dual limbic divisions. In more complex mammals, these dual modes of memory consolidation are not only linked to unique controls on action but also seem to have evolved specific capacities in cognitive representation, supporting the holistic representation of context in the dorsal division, or the focused differentiation of specific items and objects in the ventral division.

Dual frontolimbic methods of motive self-regulation

Although the cognitive capacities of the dual limbic divisions involve posterior perceptual integration as well as the organization of action in frontal networks, it is in the frontal networks where the motivational controls are more obviously differentiated. In humans, these motivational controls are not limited to elementary learning processes, but are integral to the more complex patterns of self-regulation in personality. Thus, there is a direct alignment of the dual modes of action regulation with more general qualities of behavioral regulation. The dorsal division contributes to the impulsivity and loose self-regulation that is characteristic of extraverts, whereas the ventral division provides the constraint and tight self-regulation that is characteristic of introverts (Eysenck, 1973; Passingham, 1970).

The involvement of unique motive biases associated with the dual modes can be seen in classical observations on the differential effects of dorsal versus ventral frontal lobe lesions on personality. The "disinhibition syndrome" associated with frontal lesions in the traditional neuropsychological literature is specific to ventral frontal (orbital and ventrolateral) lesions (Blumer & Benson, 1975; Damasio, 1998). Because orbital frontal lesions cause a loss of the normal constraint of impulses, Blumer and Benson have described this as the *pseudopsychopathic syndrome*. The implication for normal personality is that, when it is normally intact, the ventral frontolimbic circuit contributes what may be described as an *internalizing bias*, applying the modulation of anxiety, vigilance for threat, and the constraint of impulses to the ongoing mix of self-regulatory operations.

In contrast, lesions that are specific to dorsal frontolimbic networks (anterior cingulate and mediodorsal frontal cortex) lead to a *pseudodepression syndrome* (Blumer & Benson, 1975; Flor-Henry, 1984). When anterior cingulate and medial frontal lesions are extensive and bilateral, the loss of behavioral initiative leads to an *akinetic syndrome*. That the integral motive bias for movement in the dorsal pathway is a positive

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one is shown by what appears to be a depressive syndrome with mediodorsal frontal lesions. It is accurately described as pseudodepression, because it is caused by brain damage and not an affective disorder. The implication for normal personality is that the dorsal frontolimbic pathway normally provides what may be called an *externalizing bias* to self-regulation, acting impulsively in service of positive hedonic urges.

Multileveled Motive Control of Mood, Arousal, and Neural Plasticity

The differential roles of the dorsal and ventral limbic systems can thus be seen to influence experience and behavior at multiple levels of analysis, including elementary learning biases, the control systems for action, and more general capacities in the person's self-regulation in the social context. Through influencing these several aspects of the child's orientation to the environmental context, these dual limbic modes of learning and self-regulation can be described as neurodevelopmental processes, orienting the brain's growth toward the dual complementary functions of externalizing and internalizing. The important insight is that the development of psychological function is identical to the process of neural development. As a result, the same motive process that guides neural development guides the psychological self-regulation of learning, motivation, and cognition.

At the most basic level, neurodevelopmental control emerges from the elementary neuromodulator systems of the vertebrate brain, systems that we have traditionally understood as arousal controls. What has been poorly recognized is that these systems have inherent affective biases, changing the individual's mood state as soon as they are engaged. These neuromodulator control systems seem to have been integral to the differential evolution of the mammalian corticolimbic networks, differentiating the dorsal and ventral modes of motivated cognition. By biasing experience and behavior through coherent motive modes, these neurodevelopmental mechanisms can explain the psychological functions of extraversion and introversion that are integral to normal neuropsychological development. When these functions are overly exaggerated or become disorganized, we recognize them as the symptom patterns of externalizing and internalizing in developmental psychopathology.

Controlling neural arousal

In mammals, the control of neural arousal is achieved through several neuromodulator systems, including norepinephrine from the pontine locus coeruleus, serotonin from the brain stem raphe nuclei, dopamine from the midbrain ventral segmental area, and acetylcholine from both the brain stem and the basal forebrain (nucleus basalis) control nuclei (Aston-Jones & Cohen, 2005; Cooper, Bloom, & Roth, 1974; Mesulam, Mufson, Levey, & Wainer, 1983). A balance or inhibitory influence for these arousing or activating effects seems to be provided by the serotonergic pathways (Tops, Russo, Boksem, & Tucker, 2009). Mammalian evolution has extended that of the vertebrate brain by elaborating on the control properties of primitive arousal regulatory systems. In mammals, the integrated telencephalic–diencephalic circuits that we have described as the dorsal and ventral limbic systems can be seen to organize the complex functions of thalamic, hypothlamic, striatal–pallidal, and corticolimbic circuitry on the basis of the cybernetic properties of specific neuromodulator systems, some of which (norepinephrine and serotonin) seem more important dorsally, and others (dopamine and acetylcholine) more important ventrally (Tucker & Luu, 2012).

An important theoretical challenge is to understand the anatomical lineage that connects the more recently evolved circuitry of the human telencephalon and cerebral hemispheres to the motive controls emergent from the subcortical neuromodulator systems. We briefly outline the modern progress in understanding the limbic system. An important insight is that the motivational control of the mammalian hemispheres involves not only the limbic cortex or nuclei (piriform cortex, cingulate cortex, hippocampus, and amygdala) but also major amygdala–striatal–pallidal and septal–hypothalamic circuits, each of which has unique connections with brain stem reticular activating systems. We then point to our own theoretical approaches to considering the origins of the dorsal and ventral divisions of the limbic system with specific neuromodulator systems. From a theoretical perspective, it is important to understand the continuity of multiple levels of motive and cognitive regulation with the elementary properties of the neuromodulator control systems.

The psychological challenge is explaining the integral role of mood states and qualities of neural arousal that differ between the psychological functions of extraversion and introversion. An important clue is that the control of arousal involves mood-altering neuromodulators. One major neuromodulator system (norepinephrine) appears to bias cognition toward the mood state of elation (in extraversion). Another one (dopamine) biases the mood state toward anxiety (in introversion). In this admittedly simplistic outline, the dimensions of affect in the psychological literature (positive affect and negative affect, or extraversion and neuroticism) can be seen to align with the dimensions of neural arousal, involving *elation* (a depression–elation dimension) for the norepinephrine modulation of the dorsal limbic system and *anxiety* (a calm to anxious dimension) for the dopamine (and likely acetylcholine) modulation of the ventral limbic system (Tucker & Luu, 2007).

In addition to these integral affective biases, the neuromodulator systems apply integral controls to neural activity in time. The norepinephrinergic motive basis of the dorsal limbic system involves a *habituation bias*, where neural activity attenuates rapidly, such that novel events are required to maintain attention. The dopaminergic motive bias of the ventral limbic system involves a *sensitization* or *redundancy bias*, where neural activity is sustained within the processing network and focused on a consistent set of elements. These

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dual regulatory influences, these neurocybernetic methods, can be seen to have widespread effects on the regulation of learning and memory differentially in the dorsal and ventral limbic systems.

The multilevel organization of motivated cognition

In the control of cognition in the mammalian cerebral hemispheres, memory consolidation requires the same limbic network (Zola-Morgan & Squire, 1993) that carries out motivational control (Tucker & Luu, 2007). Whether cognition is related more to sensory or to motor functions, memory consolidation requires that the relevant cortex is regulated by its connections with the limbic system (Mishkin, 1982). The limbic system, in turn, appears to regulate its activity through interactions with the brain stem reticular activating system (Pribram, 1981). These reticular (netlike) circuits assemble top-down influences in elementary ways that are then used to guide the activity of the brain stem and midbrain neuromodulator control systems that then project upward through the diencephalon and cerebral hemispheres to alter the arousal and function of the entire telencephalon (Moruzzi & Magoun, 1949).

The concept of the limbic system has long been a contentious issue in neuroscience (Heimer et al., 2007; MacLean, 1990). Furthermore, as recognition of relevant subcortical as well as cortical circuitry developed over the years, it has sometimes seemed that the concept of the limbic system would continue to expand until it covers the entire brain (Brodal, 1969; Heimer et al., 2007). One of the first and more important expansions was provided by Nauta and associates (Heimer & Nauta, 1969; Nauta & Haymaker, 1969), whose anatomical studies showed the extensive interconnections of the major limbic circuits with the hypothalamus, as well as with the reticular networks of the brain stem. The more recent characterization of extended amygdala networks, as well as the reentrant circuitry of the ventral striatum with the ventral palladium (connecting to thalamus and then cortex) by Heimer and associates (Alheid & Heimer, 1988; Heimer et al., 2007), led to an appreciation of how more elementary motivational circuitry could be recruited to support control of the more widespread corticolimbic networks.

These more modern efforts have continued a long-standing search for understanding the functional roles of subcortical circuits, such as those mediating hypothalamic controls over bodily processes, in relation to the regulatory influences exerted by brain stem activating systems over the attention and cognition of the cerebral hemispheres. In Yakovlev's (1948) summary of classical notions of neuroanatomical systems, the core of the central nervous system is organized around visceral functions, described as the "sphere of visceration." Processing throughout the neuraxis then engages in a process of *exteriorization* or negotiating between internal visceral needs and the demands and opportunities of the environmental context. A similar theme was echoed by Mesulam in his analysis of the functional organization of human neuroanatomy (Mesulam, 1990). The limbic networks are critical because, through the process of cognition, they provide mediation between internal, visceral demands and the specialized sensory and motor networks of the cortex.

From this perspective, the engagement of the circuits of the reticular activating system is critical to linking arousal controls to the motivational mechanisms of the limbic system (Pribram & MacLean, 1953; Pribram & McGuinness, 1975). With the recognition that neurochemically specific neuromodulator systems are fundamental to human motivation, as shown by evidence both from psychiatric drugs and from street drugs (Kokkinidis, & Anisman, 1980), neuroscientists faced the difficult theoretical challenge of relating specific neuromodulator control systems, including norepinephrine and dopamine, to the range of self-regulatory excesses seen in psychiatric conditions or in drug addiction (Tucker & Williamson, 1984).

A potential theoretical advance came from the recognition that the limbic system, and its extensive connections with the cortex, may not represent one system but two. Although this notion was suggested by early anatomical studies (Dart, 1934; Sanides, 1975), it was the advances in neuroanatomical methods of tracing circuits quantitatively in the 1970s by Pandya and associates that led to definitive evidence that dorsal networks of the cortex, with a limbic base in the hippocampus and cingulate cortex, were largely separate from the ventral networks of the cortex, with their base in the piriform cortex, insula, and amygdala (Galaburda & Pandya, 1983; Mesulam, Van Hoesen, Pandya, & Geschwind, 1977; Pandya, & Seltzer, 1982; Pandya, Seltzer, & Barbas, 1988; Pandya, Van Hoesen, & Mesulam, 1981). In considering the evidence on differing learning biases of the dorsal and ventral divisions of the limbic system (Liotti & Tucker, 1994; Tucker, 1993), it became important to understand how these major functional divisions of the mammalian brain may be regulated by different neuromodulator control systems.

The neurocybernetic method of habituation

The locus coeruleus norepinephrine (LC-NE) system may be particularly important to the dorsal division of the limbic system and cortex (Tucker & Luu, 2007). Locus coeruleus projections are dense within the dorsal cortex, proceeding to the frontal pole and then caudally throughout the dorsal hemisphere (Morrison, Foote, Molliver, Bloom, & Lidov, 1982). Whereas norepinephrine modulation is absent for the striatum and pallidum, it is strong for the medial septum of the dorsal limbic circuitry, which in turn includes projections to the medial preoptic nucleus of the hypothalamus that may be particularly important in regulating cerebral arousal (Berridge & Waterhouse, 2003). Similarly, the prefrontal control over the LC-NE system involves projections from the dorsomedial and dorsolateral, but not orbital (ventral), frontal cortex (Arnsten & Goldman-Rakic, 1984).

Key functional capacities of the dorsal limbic system may reflect modulation by the norepinephrine projections. The

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observation of increased metabolites of norepineprhine during the manic phase of bipolar disorder, and decreased metabolites in the depression phase, originally suggested a link between norepinephrine and mood control (Schildkraut, 1965). Although norepinephrine has been implicated in anxiety, this interpretation seems to have drawn on the general link between increased arousal and norepinephrine activity, rather than a specific engagement of the LC-NE system in aversive arousal (Berridge & Waterhouse, 2003).

In addition to the tonic increase in locus coeruleus neuronal activity in waking states, there is a phasic response of the LC-NE system in response to novel events (Aston-Jones, Ennis, Pieribone, Nickell, & Shipley, 1986). The response to novelty appears to occur because the phasic activity of the locus coeruleus system habituates rapidly to stability in the environment. In considering the cybernetic properties of what they described as a *habituation bias*, Tucker and Williamson (1984) suggested that the active effect of this influence on attention would be to create an expansive scope, because diverse elements of the surround would each receive brief, and rapidly habituated, processing. This mode of attention control may be integral to the spatial cognition and memory of the dorsal corticolimbic networks (Tucker & Luu, 2007, 2012).

The habituation bias may be congruent with the impulsive, feedforward mode of action regulation in the dorsal networks, and with the gradual mode of learning integral to the hedonic context model (Tucker & Luu, 2007, 2012). With rapid habituation, the phasic response of the norepinephrine mode of regulation would be suited to continual shaping of the context model, but not to focused attention.

These several features of norepinephrine control, including the elated mood, the habituation bias, the expansive attentional scope, the impulsivity of action, and the gradual learning of the external context, may comprise the self-regulatory mode of extraversion. Certainly the entire hierarchy of the dorsal limbic circuits and cortical networks is involved in an integrated functional system. However, this system may be dependent on a primitive yet effective neurocybernetic method, emergent from the rapid habituation of neural response to environmental events.

The tuning of cerebral networks to be responsive to input, yet to decrement rapidly, could be seen as a kind of homeostatic neural plasticity. Norepinephrine is critical not only to regulation of neural development in the fetus (Marin-Padilla, 1998) but also to the control of critical periods, such as in the visual system (Bear & Singer, 1986). However, this is not a homeostatic control in the sense that it restores the capacity of cerebral networks that has been taxed by ongoing learning (Turrigiano, 2007). Rather it is a control that sets the tone or mode of learning. In this sense, the norepinephrine habituation bias may be a form of *allostatic* neural plasticity (Luu & Tucker, 2003a, 2003b), in that the elementary neurocybernetic method of response with rapid habituation biases the propensity for synaptic learning in the circuit in a way that has unique adaptive properties that have been integral to the evolution of the dorsal pathway in the mammalian brain.

The neurocybernetic method of sensitization

In designing autonomous systems, the cybernetics of feedforward control, as in the mammalian externalizing that we have just described, are essential but incomplete unless the system has complete knowledge of the environment (Hendler, 1995). Without complete knowledge, ongoing adjustment is necessary, such that feedback control is also required to constrain behavior in response to environmental events that turn out to be discrepant with the system's predictions from its context model. In the mammalian brain, feedback control appears to be provided by the ventral corticolimbic pathway, with important guidance from not only the amygdala but also the striatal–pallidal (thalamocortical) circuitry. The midbrain dopamine neuromodulator systems appear to be integral to the unique cybernetics of feedback control through a *sensitization* or redundancy bias, including the substantial nigra for motor control and the mesolimbic ventral segmental area projections for limbic and motive control (Tucker & Williamson, 1984).

The difficulty of interpreting the functional roles of neuromodulators has perhaps been most clearly demonstrated in the divergent scientific accounts of dopamine function in the mammalian brain (Berridge, 2007). The dopaminergic projection systems are clearly integral to what was initially conceived as the reticular activating system, such that animals with dopamine deficiencies are severely impaired in motivational and behavioral initiative, and therefore must be kept alive artificially (Berridge, 2007). Because dopamine modulation appears to be enhanced strongly by stimulant drugs such as amphetamine or cocaine (Kokkinidis & Anisman, 1983), an influential interpretation has been that dopamine mediates the brain's reward system (Wise, 1989).

However, from the earliest observations of the time course of neuromodulator changes in response to stimulant drugs (Kokkinidis & Anisman, 1983), it was clear that for humans the rush of elation with the initial bolus of the drug was due to norepinephrine, which quickly depletes in a manner consistent with rapid habituation, such that norepinephrine metabolites are then depleted in the addict's depressive or crash phase. In contrast, the more extended dopaminergic modulation following the amphetamine dose is associated with the vigilance and paranoia of the chronic addict's strung out condition (Tucker & Williamson, 1984). The fundamental motive control associated with this phase of dopaminergic modulation, the state of anxiety, would be sufficient to explain other features of dopamine's influence, including motor priming, the facilitation of habit formation in learning, and the bias toward behavioral stereotypy at high doses of dopamine agonists. Tucker and Williamson (1984) described the qualitative neural control applied by the mesolimbic dopaminergic system as the *redundancy* or *sensitization bias*.

This evidence on the effects of human stimulant abuse was well documented in the scientific literature, and was

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consistent with the systematic manipulation of norepinephrine and dopamine in animal studies (Tucker & Williamson, 1984). Nonetheless, the notion of mesolimbic dopamine as mediating reward and drug addiction persisted through the later decades of the 20th century in both human and animal neuroscience literatures, even though there was no solid evidence of dopamine supporting pleasurable states (Berridge, 2007, 2009; Ikemoto, 2010). A clear recognition of the separation of dopamine's influence from a general reward was made in Berridge's (2009) differentiation between dopaminergic enhancement of *incentive salience*, a state of "wanting" in contrast to reward or pleasure, which was described as a state of "liking."

In a recent review, Berridge (2007) has updated this distinction between reward and incentive salience. In considering this model, we suggest that the "wanting" or incentive salience notion characterizes a similar state of motive anticipation as the psychological construct of *anxiety*. Berridge (2007) points out that, because animals with genetic damage to dopamine neuromodulation are still capable of elementary learning (even though they must be kept alive artificially), dopamine is not essential to learning. While this evidence is relevant, learning effects are not necessarily reflective of just one neural mechanism, and the residual learning in these animals may reflect the unimpaired dorsal corticolimbic learning and consolidation capacities. There seems to be no reason to ignore the evidence that dopamine neuromodulation not only responds to stress but also enhances components of learning, such as habit formation, the *stamping-in* of learned behavior, and the specific detection of discrepancy from expectations, as reflected in the Rescorla–Wagner model or in more recent temporal difference models of learning (Schultz, 1997). These multiple effects are compatible with the notion of a redundancy or sensitization bias of a qualitative modulation of a ventral limbic motive state that in human experience would be described as anxiety.

Thus higher brain systems seem to have evolved complex capacities, including memory consolidation, attention, and cognition, that elaborate the specific cybernetic properties of the dopaminergic sensitization bias. A key point may be the integral role of dopaminergic control in the striatal circuitry, including not only the substantial nigral control of the motor sequencing of the dorsal striatum but also the mesolimbic ventral tegmental dopaminergic control of the ventral limbic system and the ventral striatal–pallidal circuitry. As the ventral cortex evolved its capacity in object cognition, the focusing of neural processing by the primitive control of the sensitization bias may have been a key factor. An object is represented through focal attention and inhibition of other competing elements in the perceptual or conceptual surround, just the properties of neural activity in time that may be facilitated by a sensitization bias. When this mode of cognition is engaged together with the aversive affective bias of anxiety and vigilance, the effect may be a motive state of *introversion* that is integral to regulating the process of neural development, and that is an essential complement to the neurodevelopmental motive process of extraversion (Tucker & Luu, 2012).

Motive control in context

We have thus outlined a theoretical model in which there are primitive controls that have evolved in the vertebrate brain to modulate neural activity in time. These controls have remained integral to the more complex networks for memory consolidation and cognition in complex mammals, including humans. The LC-NE system supports a habituation bias that is integral to the motive state of elation and to expansive attention, and that facilitates a mode of self-regulation that is both impulsive and extraverted. This mode appears to be integral to the externalizing disorders in child behavior problems. The ventral segmental area dopamine system supports a sensitization bias that is integral to anxiety, that supports focused attention, and that facilitates a mode of self-regulation that involves both self-constraint and psychological introversion. This mode appears to be integral to the internalizing disorders of developmental psychopathology.

Although these dual modes of neural and psychological functioning have evolved to be complementary, and appear to be more or less balanced in normal development, they are not simultaneously active. Normal development seems to involve certain periods, such as the infancy of the first year, in which extraversion is dominant. In other periods, such as in the increasing autonomy of the second year, introversion becomes more important. Understanding the differential demands for these modes of self-regulation during the process of self-organization may suggest theoretical insights into critical periods for developmental psychopathology.

The Critical Period of Embryogenesis

The most important and remarkable transformations in neural development occur before birth, as the infant human brain emerges through progressive transformations of the vertebrate phyletic program (Gould, 1977). In this process of neuroembryogenesis, the neuromodulator control systems appear to play integral roles in guiding the neural activity that is critical to the differentiation of neural architecture at several stages of brain development. Among the findings of recent research into embryological neural development, there are several clues to the differential organization of the dorsal and ventral divisions of the mammalian brain, with implications for understanding the phylogenetic as well as the ontogenetic origins of the motive processes of externalizing and internalizing. In broad outline, the neurodevelopmental mechanisms of externalizing have important roots in the pallium, the primitive three-layered cortex of reptiles and amphibians. Those of internalizing can be seen to emerge from the anlagen or primitive tissues of the subpallial basal ganglia (Tucker & Luu, 2012). With these primitive phyletic origins, the unique neurocybernetic modes of organizing neural development in

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embryogenesis appear to continue to organize the child's self-regulation in social and psychological development.

Pallial roots of the pyramidal architecture of the dorsal cortex

The formation of the cerebral cortex involves migration of neurons that are formed at the edge of the ventricles in the core of the hemispheric tubes (the ventricular zone). These neurons then migrate outward to take up positions in the layers of the cortex (Rakic, 2009). In its early embryonic stages, the mammalian cortex appears similar to the pallium (primitive three-layered cortex) of amphibians and reptiles. It is dominated by pyramidal cells, which migrate to the superficial layers and become integrated into the local architecture under the influence of norepinephrine (Marin-Padilla, 1998). As recognized by Lorente de No, this pallial organization remains integral to the mammalian hippocampus. In certain interesting respects, architectural features of the pallium, dominated by norepineprhine control, glutaminergic pyramidal function, and the three-layered organization, will remain as outstanding features of the dorsal cortical limbic architecture in the mammalian brain, even as it becomes articulated into the full six-layered mammalian architecture (Tucker & Luu, 2012). The dorsal cortex will become regulated particularly by the *matrix* component of the thalamic input (Jones, 2007), involving calretinin neurons migrating from the ventricular zone (Rakic, 2009) to the cortex, and providing thalamic control over interregional integration of the cortex (Jones, 2007). This unique thalamic control may become important to the holistic attention and spatial memory of the dorsal corticolimbic division (Tucker & Luu, 2012).

Subpallial roots of the granular architecture of the ventral cortex

With the normal progress of mammalian neuroembryogenesis, the three-layered form differentiates to the six-layered architecture, as thalamic input to Layer 4 becomes an organizing influence in establishing the six-layered network (Marin-Padilla, 1998). Several lines of evidence suggest that the formation of the six-layered mammalian architecture involves substantial input from the ganglionic eminences, the subpallial anlagen of the vertebrate telencephalon, the basal ganglia (Rakic, 2009). Furthermore, the neuronal migrations from the medial and lateral ganglionic eminences, and not the ventricular zone, will be important to the ventral divisions of the cortex specifically, with their granular architecture reflecting the extensive development of the Layer 4 thalamic input (Tucker & Luu, 2012). The GABAergic interneurons that are critical to the network function of the mammalian cortex generally, and to the parvalbumin neurons of the *core* thalamic projections supporting the ventral cortex particularly, also derive from the ganglionic eminences (Rakic, 2009). These critical complements appeared to fuse with the pallial pyramidal architecture in the evolution of the mammalian six-layered cortex, thereby providing the essential inhibitory control of the mammalian cortex through incorporation of subpallial, basal ganglia, material (Tucker & Luu, 2012).

Embryonic organization through dual neurocybernetic modes

The pattern of embryological development thus suggests dual origins of the dorsal and ventral divisions of the cortex and the associated limbic circuitry. The dorsal corticolimbic networks appear to reflect the widespread excitatory cellular architecture and unique (norepinephrine and calretinin matrix) network function of the vertebrate pallium. This architecture and function may remain integral to the cognitive capacities and neurodevelopmental plasticity of the dorsal division of the human brain. For example, in the feedforward, impulsive mode of motor control in the dorsal networks of the frontal lobe, the minimal influence of Layer 4 inputs, and the corresponding limbipetal (inner to outer or visceral to somatic) direction of control, implies that action regulation in the dorsal brain has the impulsive characteristic (Shipp, 2005) of externalizing (Tucker & Luu, 2012). In contrast, the inhibitory control provided by greater emphasis on GABAergic modulation and core (parvalbumin) projections to the granular Layer 4 may provide the ventral division of the cortex with a capacity for inhibitory differentiation of representations that is essential to object cognition of the ventral, granular division of the cortex and the inhibitory constraint of internalizing (Tucker & Luu, 2012).

With these deep roots in primordial phyletic algorithms of self-regulation, the developmental mechanisms of externalizing and internalizing must achieve fundamental tasks in self-organization of the human infant's neural architecture long before birth. These are in large part epigenetic mechanisms, mediating neuronal function not only through gene transcription but also through many functional interactions, including essential ones mediated by neuromodulator controls. As a result, we can see how the neurodevelopmental mechanisms of externalizing and internalizing reflect the residuals of the pallial and subpallial modes of self-organization. These primordial neurocybernetic algorithms may provide an essential continuity to neuroembryogenesis, affording canalization of coherent function (Waddington, 1942) to the extensive genetic variability of the human genome (Tucker, Luu, & Poulsen, in press).

This theoretical model of the origins of externalizing and internalizing may involve a certain degree of speculation. Nonetheless, it seems clear that embryogenesis must be seen as the most critical period, resulting in temperamental differences predisposing the child to unique patterns in responding to the developmental challenges of life after birth. However they emerge in development, the temperament differences observed in young children can be seen to reflect a continuing challenge to balance the biases toward externalizing and internalizing (Achenbach, 1982), shaping the course of psychological development and simultaneously determining both cognitive and social capacities.

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Self-Regulation Through Attachment and Individuation

In the first weeks and months of life, the human infant must establish a secure bond with the parent or caregiver. It is this interpersonal attachment that serves as the essential supporting context for the infant's own emerging self-regulatory capacities, beginning with the task of obtaining nourishment. The child's neural architecture for both motive self-regulation and memory consolidation can be seen to be formed through a kind of negotiation, between visceral (homeostatic) functions at the limbic core of each hemisphere and the somatic (sensorimotor) domain of behavior organized in the sensory and motor cortices.

For the infant, this ongoing negotiation between visceration and exteriorization (Yakovlev, 1948) must be organized within the embedding context of the parent's support. Both psychoanalytic and academic developmental theorists have recognized that the child's self-regulation, such as in managing distress, is ineffective in the early stages, such that the parent's capability for supporting the child's own self-regulatory process becomes an important influence on psychological development (Fonagy, 2000; Mahler, 1968; Rothbart & Posner, 2006). For the developmental psychoanalysts, the parent's assistance in self-regulation becomes incorporated with the continuing contribution of personal relations to the organization of the self (Fairbairn, 1994; Hazell, 1977; Kohut, 1978).

From the point of view of neurodevelopmental theory, the early experiences of attachment and self-regulation form the network architecture that will be the foundation of neural and psychological self-regulation through each succeeding life stage. The period of early infancy can then be characterized as a critical period, in that the results of the synergy of self-regulatory capability with social interaction will shape neural development in lasting ways.

Simply by considering the nature of activity-dependent plasticity in forming cerebral networks, it becomes clear that brain development is cumulative. Each stage of development lays a foundation for the next stage, and this foundation becomes progressively less modifiable as the next stage takes shape. The close of a critical period is then marked by brakes on neural plasticity that complete the neural architecture of that period and prepare for further growth (Takesian & Hensch, 2013).

Certainly the abrupt transitions in the neurodevelopmental process seen at the close of critical periods in the maturation of the sensory cortex may be more abrupt than those in the more general visceral and motive self-regulatory capacities of the limbic system and subcortical circuits. It is the continuing plasticity within limbic networks that appears to provide the extended developmental period for the human brain (Barbas, 1995). Yet the maturation of the infant brain involves a relative close to fetal neural plasticity. Because development is cumulative, any deficits in the basic capacity for self-regulating needs and expectancies within a supportive interpersonal context in infancy can be seen to lead to inadequacies in coping with the challenges of self-regulation in each subsequent stage of neural and psychological development.

The primordial comfort of secure extraversion

It is in this more general sense that the child's development in the first year can be seen as a critical period for the externalizing process. Mammalian infants appear to form attachment through motive processes mediated by opiate mechanisms (Panksepp, 1981, 2003; Tucker, Luu, & Derryberry, 2005), providing powerful motive mechanisms that are intrinsic to social contact and require no mediation by hunger or feeding (Panksepp, Siviy, & Mormansell, 1985). In addition to what appears to be norepinephrine mediation of the elation of social arousal in the infant's behavior, externalizing may be organized around the fundamental hedonic value of opiate-mediated comfort of contact with the parent (Tucker et al., 2005).

Thus, the specific neurocybernetic method of extraversion appears to provide the necessary close alignment of the infant's internal representations with the flux of the social world. This close alignment also involves the motor component of extraversion, the immediate and impulsive expression of internal urges in behavior.

As psychoanalytic therapists searched for the developmental origins of their patients' most basic personal and interpersonal insecurities, it was the earliest experiences of an infant's attachment that seemed to provide the only adequate explanation (Hinshelwood, Robinson, & Zarate, 2011; Mahler, 1968). Although such complex historical processes are difficult to research, modern developmental psychology studies continue to confirm the importance of the early attachment relation, with essential contributions from not only the parent's skill and resources but also the infant's temperament (Derryberry & Rothbart, 1988; Rothbart & Posner, 2006).

Controlling autonomy and attention through introversion

The second year of life may be a critical period for internalizing, in both the psychological and neural components of this neurodevelopmental process. The maturation of the internalizing process may be seen in the increasing motor coordination of the older infant, culminating in increasingly effective locomotion. The affective components of internalizing also mature during this interval (6–18 months), with both anxiety and hostility playing increasing roles in regulating the personal and interpersonal behavior of the toddler. These motive processes are essential for the individuation of personal autonomy, providing foundational skills that will allow the developing child to arbitrate social influence in many future contexts (Mahler, 1968).

From the perspective of neurodevelopmental theory, it is useful, not to compartmentalize the functions of motivation, affect, and interpersonal behavior, but to recognize that the neurodevelopmental process is itself under motive control. As a result, the exercise of autonomy is an integral feature of the sensitization of neural activity, the focus of attention,

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and the effortful control of behavior that emerges from the internalizing process (Tucker & Luu, 2012). Cognitive development is then but one manifestation of the neurodevelopmental process, with the several related skills in cognitive control dependent on the primitive adaptive control of the sensitization bias. For highly anxious or autistic children, whose self-regulation is pathologically biased toward internalizing, cognition may be ineffective in guiding interpersonal interaction, but it gains a highly focused, and highly skilled, capacity for object manipulation through the continual modulation by the sensitization bias.

Developing intelligence by social assimilation and accommodation

Certainly the exaggeration of one mode or the other may be an obvious manifestation of the psychopathology as a poor developmental outcome of these critical periods. More important may be the lasting deficits that result from inadequate incorporation of the foundations of externalizing or internalizing. By the time the child is a toddler, there should be a strong foundation for social cognition that has been formed through exercising both these modes. This foundation may be an integral basis for the social basis of intelligence throughout the developmental process, with externalizing supporting the assimilation function and internalizing providing the neural substrate for accommodation (Piaget, 1992/1936). Although Piaget emphasized these processes as general conceptual ones, they must work in the social context, where knowing how to relate requires considerable cognitive skill.

For example, the capacity for understanding the perspectives of others appears to emerge through intersubjectivity, the sharing of perspective and intention that older infants naturally accomplish with parents and caregivers (Fonagy, 2000; Trevarthen, 1984). Understanding the meaning of words, for example, is accomplished in large part through understanding the mother's intention in the context in which the word has been spoken (Baldwin et al., 1996). Just as intentionality is a core motive basis for externalizing (Tucker, 2007), the child's participation in the mother's intentionality is achieved through extraversion, through building and holding an intuitive representation of the mother that includes her actions and meanings. This may be the social context for Piaget's notion of assimilation, because concepts are highly sensitive to the flux of social communication. In contrast, for autistic children for whom the capacity for extraversion becomes severely impeded by the pathological dominance of internalizing, the child cannot intuit the context of interpersonal intentions that gives meaning to interactions (Aitken & Trevarthen, 1997; Nagy et al., 2010).

Thus, a neurodevelopmental analysis may shed light on the nature of the cognitive capacity that is organized by effective infantile extraversion. Just as the dorsal corticolimbic pathways in animal learning studies are found to provide a context model, the child's dorsal corticolimbic division may provide a similar context model, a holistic understanding of self-in-context that is essential for development of the neural substrates of both the self and social cognition (Tucker, 2007).

There is no substitute for this context model that conceptualizes self in the expected pattern of social relations. The internalizing process builds knowledge of objects, and of action routines, but these are isolated, without context. Although internalizing creates autonomy, it does so destructively, through negating the dependency relation. Yet the dependency relation is integral to the foundations of the self in the mode of extraversion, engaging the context model of self in relation. Because the internalizing function is inherently destructive, differentiating the negativistic toddler from parents and caregivers, an essential complement to internalizing and autonomy, is then the rapproachment (Mahler, 1968), the reestablishment of the secure dependency relation (and the context model) in the presence of autonomy strivings.

Early childhood can thus be considered as involving critical periods for externalizing and internalizing, periods during which these functions are less balanced than they will be at any point later in normal development. Although alternation between the modes of extraversion and introversion seems to be the normal psychological process, the integration and balance of these modes may be the major task of childhood. Conversely, the failure to integrate these modes within personality may lead not only to an exaggeration of extraversion or introversion but also to the inability to use both modes when they are highly charged yet need to be integrated in understanding a difficult situation. In the phenomenon of *splitting*, as seen in borderline and narcissistic personality disorders, the person can only adopt one or the other mode, leading to a highly ambivalent and disorganized course of relating (Fonagy, 2000). Others are experienced as primitive projections of charged childhood templates, all good and gratifying to the self, or all terrible, frustrating, and evil threats to the self (Hinshelwood et al., 2011).

The relational tools of cognition

Thus, we can theorize that for the normal child, the self is organized through neurodevelopmental motives of both extraversion and introversion, organizing the corticolimbic systems of memory and cognition to support not only family and peer relations but also cognitive development. In the educational setting, for example, a degree of extraversion may be integral to being receptive to the influence of the teacher, as the child identifies with the teacher's perspective and incorporates the received knowledge in her own thinking. The child's context model integrates the increasing knowledge of the world encountered through the educational process.

Internalizing is also essential in the early school years, because the child must gain the discipline of self-constraint, inhibitory control over behavior, and the focused attention that supports routinized cognition (Luria, 1973). These are skills that become "internalized," but largely through the processes of socialization. For the normal preschool child, whose primary mode of self-regulation involves considerable

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externalizing, the tasks of the classroom involve a new degree of internalizing skills. In what may be considered a new critical period for internalizing in the early school years, the skills of self-discipline are gained to a considerable degree through social learning, as the child internalizes the regulatory constraints applied by parents, teachers, and to some degree through observation of other children (Dishion, Nelson, Winter, & Bullock, 2004). In addition, the mode of introversion is essential for critical thinking. Even for the child in the primary grades, a critical attitude provides the opportunity for autonomous thinking about significant issues.

Thus, the increasing intelligence gained through education and life experience in the childhood years can be understood to be organized by multiple neurodevelopmental processes, including the modulating of waking arousal (with habituation and sensitization biases), with inherent affective tones (elation and anxiety), and with not only cognitive (expansive versus focused attention and memory consolidation) but also inherent interpersonal (extraversion and introversion) orientations (Tucker & Luu, 2012). Even as we emphasize the neurodevelopmental basis for the child's differentiation of increasingly complex neuropsychological domains of the self, the interpersonal arena remains the defining context for attachment, individuation, and the organization of personality.

Crystallizing Identity in Adolescence

In mammalian development generally, sexual maturation reflects the end of the juvenile period. Whereas the juvenile period involves an embryonic-like neural plasticity to allow extended learning under parental guidance, sexual maturation must signal the beginning of adult functioning, with effective execution of the mature behavioral repertoire. In broad terms, the mammalian juvenile period can be seen as one dominated by externalizing, a process of learning adaptive behavior in a protected context. The young mammal may be described as extraverted, in that cognition is oriented strongly to observational learning. Supporting the capacity for observational learning is the motive for play. Play involves free and impulsive behavior in service of an extraverted sensual capacity, providing the young animal with extended exercise of conceptual as well as sensory and motor skills.

In contrast, with sexual maturation there is a new requirement for internalizing, as the neural plasticity of the juvenile period is closed, and the mature animal engages in a more focused mode of coping, through the constrained and routinized tasks of survival and reproduction.

For the human child, the transition to adult brain function in adolescence may involve a similar termination of neural plasticity, with an increasing internalization required for the crystallization of an adult identity. In this maturational process, major forms of psychopathology, such as bipolar disorder, schizophrenia, borderline personality disorder, and psychopathy, appear in increasingly articulated manifestations that are not seen in childhood. To understand the emergence of the adult forms of psychopathology, it may be useful to consider adolescence as a new critical period, with new challenges for the neurodevelopmental processes of internalizing and externalizing.

Although both biological maturation and social adjustment are defining boundaries of adolescent development, the core process is psychological: the crystallization of an identity. The self becomes a particularly important unit of analysis for the scientific study of adaptation and psychopathology in adolescence. As a psychological construct, the self is difficult to reduce to either the biological mechanisms or the social exchanges that shape the adolescent's neuropsychological integrity.

This is not to say that a concept of the self cannot be framed in biological terms. Some notion of self is needed from the outset of development, to explain the coherence of the epigenetic mechanisms that regulate the systems-level organization of the embryo's development. Furthermore, the social nature of neural maturation becomes evident as we recognize that the child's psychological identity comprises incorporation of both parental qualities and directives and the formative exchanges of peer interactions.

Yet neither biology nor the social context provides an adequate explanation: a psychological analysis may be essential. The self is the venue for the epigenetic coherence of the developmental process. Implemented in each moment by neurophysiological mechanisms, it is the motivated and self-correcting framework for adaptive progress. Always embedded in a social matrix, to be sure, the self becomes increasingly autonomous by necessity in the adult transition.

Increasingly in the early adolescent years, and in ways that were largely implicit in childhood, the self becomes conscious. Particularly when articulated with the new capacity for abstract thought, the adolescent's own self-evaluation becomes a powerful influence on the neurodevelopmental process. There is a new integrity of the personality that may be possible for the successfully developing adolescent. Yet this must emerge in the context of whatever traumatic residuals are left by the challenges and disorders of early childhood.

Temperamental vulnerability and the adolescent transition

Adolescence can thus be seen as a kind of metamorphosis, with not only new capacities for obtaining developmental coherence through psychological self-organization but also new risks for disorder if the systems of the self fail to achieve the dynamic balance of externalizing and internalizing with the social context (Tucker & Moller, 2007). Each child enters the adolescent transition as a new critical period of promising change, but with adaptive constraints set by the self-regulatory resources achieved in childhood.

Both genetic and epigenetic mechanisms develop during childhood to increase either vulnerability or resilience to psychopathology during adolescence and adulthood. These mechanisms can increase the sensitivity of the organism to either positive or negative experiences. Furthermore, rather

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than just a bias toward internalizing or externalizing as modes of coping, children may vary in their overall rigidity or flexibility in self-regulation. For example, Oberlander (2012) argues in his review on the role of serotonin in brain development that mechanisms such as variation in serotonergic function may best be characterized as factors of plasticity, rather than simply vulnerability to disorder.

Another example is provided by recent evidence on early institutional deprivation. A study of Romanian children who had been institutionalized, and then adopted, found that emergence of emotional problems and psychopathologies in adolescence was influenced by multiple factors, including the child's genotype, the severity of early deprivation, and the number of stressful life events during adolescence (Kumsta et al., 2010). Those children with two short alleles of the serotonin transporter gene appeared to be most plastic to deprivation in early childhood and to later stressful events during adolescence. Consistent with the idea of plasticity, rather than simply vulnerability, this group with the two short alleles and high early deprivation showed the highest increase in emotional problem scores if they experienced a large number of stressful events in adolescence (11–15 years of age), but this group showed the highest decrease in emotional problem scores if exposed to a low number of stressful life events during this period. The children with two long alleles of this serotonin transporter gene displayed the greatest resilience to emotional problems. Thus, the concept of a critical period for psychopathology may be framed by two related waves of criticality. In early childhood, adversity leads to the development of vulnerability in self-regulation. Later, during adolescence, this vulnerability may be further triggered or expressed through nonshared environmental influences (Garcia et al., 2013).

Adolescence is a period of increased independence and reliance on self-regulation, rather than regulation by others, such as parents and teachers. This independence may lead to increased exposure to nonshared experience and niche seeking that may further accelerate exposure to experiences that trigger the expression of underlying vulnerabilities in self-regulation. In a factorial path analysis of twins from the Minnesota Twin Family Study, Garcia et al. (2013) found that stable genetic influences on anxiety increased during adolescence, along with increased sensitivity to nonshared environments and decreased influence of shared environments. This evidence supports the view of adolescence as a period of increased plasticity, where interaction of experience with genetic and early epigenetic makeup accelerates both the individual's neuropsychological phenotype development and the potential expression of psychopathological vulnerabilities.

Whether vulnerability in self-regulation during the more plastic period of adolescence is expressed as psychopathologies related to internalizing or externalizing may depend in part on the type of early trauma and the child's temperament (genetic predisposition). In analysis of data from 2000 and 2007 British national surveys of psychiatric morbidity based on samples of over 7,000 respondents, Marwaha, Broome, Bebbington, Kuipers, and Freeman (2014) found that the link between early childhood sexual abuse and psychotic phenomena, including paranoid ideation and auditory hallucinations, was strongly mediated by mood instability. This dysregulation of the homeostatic balance between the two systems of positive and negative affect was also associated with high levels of dysphoria and anxiety. It is interesting that the use of psychosis scores as a continuous variable suggested that the relationship between mood instability and psychotic experience holds even across nonclinical range. These findings, therefore, further support the view that even severe psychopathologies, such as psychoses, may emerge from the dysregulation of normally adaptive mechanisms of emotional self-regulation.

Adult externalizing and the social coherence of the self

Even as each child brings unique patterns of coping to the adolescent transition, sexual maturation brings general changes in the motivational control of neuropsychological development. The general transition may be from childhood externalizing to greater adult internalizing. Yet the adolescent also engages new modes of adult externalizing, with an openness to exploring of behavioral options, particularly including adult sexuality.

Although it is an invariant component of the ontogenetic program, it is mediated in large part by the developmental timing of the gonadal hormones, such that sexual maturation itself could be seen as an epigenetic process. Whether the child's object choice emerges as heterosexual or homosexual, the psychological awakening of adult sexuality involves an important new mode of extraversion. The adolescent's experience is strongly occupied by the sexual attraction of others. Furthermore, the ability to be attractive to others becomes an essential requirement for the emerging identity. A coherent sexual identity is integral to relations not only with romantic partners but also with peers and people in general.

In early adolescence, the motive control of extraversion becomes integrated within this new context of a sexual identity. The dorsal limbic system is particularly important in the hedonic response to peer interactions and the newly charged extraversion of social arousal. As noted above, the influence of the medial septal nuclei on the preoptic nucleus of the hypothalamus appears to be particularly important to the control of the LC-NE system (Berridge & Waterhouse, 2003) and to the corresponding motive arousal of elation. The neural plasticity of the dorsal limbic externalizing function may continue to be supported by this mode of phasic arousal. Furthermore, it may be important that not only the septum but also the preoptic nucleus are important to sexual behavior, and that a dimorphism of this region has been related to human sexual orientation (Swaab, 2008). Sexual interest is paralleled by the adolescent's general interest in peer affiliation, such that effective extraversion in peer relations is an essential component of social adjustment.

The close relation between mood level and peer interactions is integral to the developmental tuning of extraversion as a neurodevelopmental process in adolescence. The

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neuromodulatory systems of the dorsal corticolimbic division, including serotonin as well as norepinephrine, appear to be responsive to the dynamics of social success, leading to momentary, or occasionally more extended, responses of elation or depression. The effect of this mood regulation may be seen not only in the social behavior of extraversion, engaging or withdrawing, but also in the developmental processes of organizing the mood-based (dorsal limbic and LC-NE) regulation of neural development. The strong mood state excursions may bias the dorsal self-regulatory systems through a kind of kindling mechanism (Harkness & Tucker, 2000; Post, 1986), such that in cyclothymic or bipolar disorders, the primitive mood state controls eventually become poorly modulated by the higher order corticolimbic mechanisms of psychological self-regulation.

Consistent with the importance of early vulnerability, the peer relations of adolescence must build on the capacity for attachment that was exercised in infancy and early childhood (Fonagy, 2000). Here extraversion is mediated by another powerful neuromodulator control, as the opiate pain system's mediation of infantile attachment (Panksepp, 2003) appears to be reengaged to direct the adolescent's strong motivation for peer attachment. The importance of this developmental motive is seen in the intense longing when peer affiliation is thwarted, and in the pathological behavior that may be related. In adolescent cutting, for example, one explanation for the self-injury is that it releases endorphins that counteract the strong deprivation of opiate neuromodulation associated with the adolescent's state of social deprivation (Tucker et al., 2005). For the adolescent as well as the infant, opiate mediation of the pain system appears to serve as a basic mechanism for attachment and belonging, bringing a powerful and immediate urgency to the extraversion of daily social relations.

Perhaps as important as the immediate influence of social and sex-role attachment on the adolescent's experience and behavior is the influence of these interpersonal outcomes and their motive processes on the developing self. Again, the childhood foundation is important. The young person who emerges from childhood with a well-integrated nascent self is likely to emerge from the challenges of adolescent peer relations with a more or less coherent identity, even when faced with more than the usual frustrations and mistreatment. What seems most important is the consolidation of a maturing identity within the context of a modicum of social acceptance. This process relies on the capacity for social extraversion as an integral component of the self. The resulting elements of the self are essential features of the dorsal limbic externalizing function: the sense of self-confidence, optimism, and agency that form an enduring motive basis for an adult identity.

Adult internalizing and the active termination of neural plasticity

The increasing development of emotional self-control in adolescence may be an integral effect of the increasing internalization associated with adult brain maturation. With sexual maturation, and with the end of the extended externalization of the juvenile period, an increase in internalization seems to be an essential motive mechanism for achieving adult autonomy. The adolescent gains a new capacity for aggression and hostility that was typically muted in childhood, but is now an essential tool for autonomous adult functioning. For most adolescents, internalizing not only involves negativistic autonomy, leaving childhood behind by breaking from dependency on the parent, but also an increasing capacity for self-discipline. This capacity provides not only the improved affective self-regulation required of adult personal relationships but also the focused attention and persistent effort needed for acquiring adult work skills. At the same time as these positive adaptive skills of internalizing emerge for most adolescents, for others internalizing disorders such as anxiety and depression appear with much greater frequency than they did in childhood.

Even though adolescence is a transition period, where considerable learning is required to adjust to the emerging adult roles, there seems to be a clear loss of juvenile neural plasticity. For sensory and motor function, this loss is striking at puberty. An example is the loss of the ability to speak a foreign language without an accent (Lieberman, 1984). In line with the gradient of early maturation of sensory and motor cortex (Yakovlev & Lecours, 1967), it is specifically the motor (articulation) and sensory (phoneme comprehension) levels of language learning that become fixed (Tucker, 2001). In line with the delayed maturation of association and limbic cortex (Barbas, 1995), many adults are able to learn the vocabulary, and to a lesser extent the grammar, of a new language, but none will achieve the sensory and motor skills required for speaking like a native speaker, in other words, someone who learned the language as a child (Tucker, 2001).

In addition to the loss of plasticity in sensory and motor cortices, adolescence is a critical period for social and cultural influence. For many young people, the close of adolescence marks the close of this critical period. In Western countries, for example, popular music preference, clothing patterns, mannerisms of speech, and hairstyles may be significant features of self-definition in the local adolescent peer culture, and they seem to be modifiable during the critical period of secondary school education. These preferences then become fixed with the loss of neural plasticity in the transition to adulthood, producing an enduring generational stratification of the culture.

The progressive loss of neural plasticity with the onset of adulthood may be mediated by active neurodevelopmental mechanisms. One of these may be the process of cortical thinning (Shaw et al., 2006). Although the initial findings have been complex, and not always consistent (Schnack et al., 2014; Shaw et al., 2008), there appears to be a progression of cortical thickening in childhood, and then thinning through adolescence and early adulthood (Schnack et al., 2014). The implications for psychological function may be suggested by correlations between intelligence scores and the timing of the

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developmental changes in gray matter. More intelligent children are apparently slower in the increasing cortical thickening in early development, but then gain greater cortical thickness later in childhood (Shaw et al., 2006). Through adolescence, the general trend is one of thinning of the gray matter of the cortex, apparently reflecting an yet unknown cellular process of neural maturation.

More intelligent young adults then show a protracted period of cortical thinning well into early adulthood (Schnack et al., 2014). Together, these findings may imply that a slower rate of maturation is associated with greater intelligence, perhaps continuing the general trend in the evolution of human neoteny (Gould, 1977). In the most recent analyses (Schnack et al., 2014), the relation with IQ scores was notably strong for regions of the left hemisphere associated with language, including the left inferior frontal gyrus (Broca's area) and the planum temporale, suggesting that the maturational trends may be relevant to uniquely human features of intellectual development.

As we have seen in the research on critical periods in neural plasticity in the development of sensory systems (Hensch, 2005a), the termination of neural plasticity for those periods appears to be an active, adaptive effect of developmental regulation. It is mediated by some aspects of neural maturation, particularly involving the parvalbumin GABA interneurons (Takesian & Hensch, 2013). Additional evidence suggests that adolescent cortical development may be regulated by similar active mechanisms in terminating the childhood period of neural plasticity. Considering the nature of these mechanisms suggests they may be related to the developmental pattern of increasing adult internalization.

Dopamine modulation is important to regulating neural plasticity generally, and we have emphasized its role in the increased redundancy of network activity, achieved in part through inhibition (Tucker & Luu, 2012). In rodents, the improvement in working memory with dopamine modulation of the prefrontal cortex (Floresco & Phillips, 2001; Seamans, Floresco, & Phillips, 1998) may be consistent with the focusing of attention with the dopaminergic redundancy bias (Tucker & Williamson, 1984). For the D_2 dopamine receptors in the cortex of rodents, the adult pattern of inhibition of pyramidal cell activity with dopamine modulation is not seen in the juvenile period. However, it emerges soon after puberty (Tseng & O'Donnell, 2007). In addition to the immediate inhibition of pyramidal activity in the prefrontal cortex associated with D_2 dopamine modulation, there is a more sustained inhibitory effect that is mediated by the fast-spiking GABA interneurons. This dopaminergic regulation of GABAergic interneurons is observed only after puberty (Tseng & O'Donnell, 2007).

O'Donnell (2010) suggests that the improved inhibitory capacity of the frontal lobe associated with the dopaminergic modulation of GABA interneurons may be important to the adult behavioral capacity of the mature animal. In considering the dopamine dysregulation hypothesis of schizophrenia, O'Donnell points out that a rat model of schizophrenia, caused by lesions of the hippocampus (the limbic base of the dorsal corticolimbic division), leads to a developmental anomaly in which the GABAergic mediation of dopaminergic inhibitory modulation fails to appear in the postpubertal developmental period (O'Donnell, 2010). If so, one interpretation is that the unregulated anxiety of acute schizophrenia may reflect the adult onset of increasing dopaminergic modulation without the balance of GABAergic inhibition. This would be a unique pathology of exaggerated and disordered internalizing.

At the same time, and perhaps as a secondary result of pathologically exaggerated internalizing, the disordered psychological function of schizophrenia can be seen as a loss of the normal externalizing function of the young adult. The common delusions of external control in schizophrenia bear a remarkable similarity to the loss of agency, such as in the alien hand syndrome, that occurs with dorsal frontolimbic lesions (den Ouden, Frith, Frith, & Blakemore, 2005). The sense of agency and self-confidence with normal extraversion can be seen as essential contributions of the dorsal corticolimbic division to the coherence of the self (Tucker & Luu, 2007). When these are lost, perhaps due to the imbalance caused by aberrant dopaminergic maturation, the coherence of the self may be severely disrupted.

Heterochronic parallels in terminating critical periods

Certainly it is difficult for rodent models to illustrate more than the most basic elements of schizophrenia. Furthermore, even the normal neurodevelopmental progression of improving frontal inhibitory control may be highly different in the adolescence of humans compared to that of rats. Nonetheless, it is striking that puberty marks a general transition in rat frontal lobe development, with the appearance of fast-spiking parvalbumin GABAergic neuromodulation, that is not unlike the pattern seen in the close of critical periods in sensory systems in several mammalian species (Takesian & Hensch, 2013).

In a broader context, it difficult not to compare these plasticity termination events to a similar mechanism of parvalbumin GABAergic maturation occurs in embryogenesis of the cortex (Marin-Padilla, 1998). This influence of internurons with the appearance of thalamic inputs reflects the transition from the pyramidal-dominant and LC-NE modulated first stage of embryogenesis, forming the (pallial-like) superficial layers of the cortex, to the second stage where thalamic input associated with the parvalbumin core thalamic projection cells (Jones, 2007) achieves the organization of Layer 4 and the full six-layered mammalian architecture (Marin-Padilla, 1998).

Further research is required to understand the significance of the apparent parallels across these widely disparate periods of neural development, embryonic cortical lamination, critical periods in sensory maturation, and sexual maturation. Nonetheless, it seems clear that the mammalian neurodevelopmental process involves mechanisms for actively terminating periods of high neural plasticity that may be as important to adequate function as the mechanism of neural plasticity

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itself. Because the earlier stages of high neural plasticity involve enhanced sensitivity to environmental influence, mediated by the pyramidal architecture under modulation by norepinephrine, we might suspect that these earlier stages involve greater externalization in the interface of the organism with the environment, consistent with a dominance of the dorsal corticolimbic division. Because the later stages of maturation involve a transition to less plasticity and a more fixed adaptive operation mediated by transitions in parvalbumin GABAergic interneuron control, we might consider these stages as reflecting greater inhibitory control associated with increasing dominance of the ventral corticolimbic division. For the human adolescent, the maturation of GABAergic interneurons under dopaminergic modulation may be consistent with the behavioral mode involving greater autonomy, focused attention, capacity for routinized action, and improved inhibitory control of impulses associated with a more adult self-regulatory pattern of internalizing.

Vertical integration and the crystallization of personal identity

The maturation of the cortex can thus be seen to be an integral basis for the adolescent's transition to adult cognition. Among the uniquely psychological capacities emerging with the human adolescent's neural development is the capacity for abstract thought (Piaget, 1936/1992). Abstract thinking allows the young adult to gain a flexibility and breadth of self-regulation through psychological processes that are not possible for the child.

More specifically, a common explanation for the adolescent's increasingly adult psychological function is the maturation of the frontal lobe. Huttenlocher (1979) observed that synaptogenesis continued in the human frontal lobe well into adolescence, after it had ceased in other cortical regions. The idea of slow maturation of the frontal lobe has become iconic in popular as well as scientific accounts, describing the adolescent's maturing urges without adult judgment and the associated self-regulatory constraint. Although the typical implication of this notion is that successful adolescents should gain adult maturity without delay, this would not fit with the finding of greater intelligence in those adolescents and young adults with a slower trajectory of cortical maturation and thinning.

Recent anatomical studies of the frontal lobe have shown that the frontal pole has undergone extensive expansion in human evolution (Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001), perhaps consistent with the notion that frontal maturation in adolescence would complete the process of human cognitive development, including the capacity for abstract thinking. However, an anatomical analysis of the connectivity of the frontal pole shows that it is not simply an expanded cortical module, but rather its functional role is defined by its extensive subcortical connections. The frontal pole is closely connected with the anterior nuclei of the thalamus, which are in turn integral to the classic Papez circuit of the dorsal limbic system (Zikopoulos & Barbas, 2006). Furthermore, the immediately adjacent orbital frontal cortex is strongly connected with the thalamic reticular nucleus, providing a pivotal point of convergence for ventral frontal cortical control of the thalamic regulation (in turn) of widespread cortical regions. Through controlling thalamic as well as limbic circuits, the frontal pole may be an important cortical network for regulating the brain stem and midbrain neuromodulator projection systems. Thus, the unique capacity of the uniquely human frontal lobe may not be an isolated cognitive module, but rather a more fully developed capacity for vertical integration, coordinating the function of multiple levels of the neuraxis.

Another example of the integral role of vertical integration in human intelligence comes from the observations on the human Forkhead box protein P2 (*FOXP2*) gene. This gene originally came to scientific attention when researchers observed language articulation deficits in families with a mutation of this gene (Maricic et al., 2013). That chimpanzees do not have the human form of *FOXP2*, and that mutations in humans produce language deficits, has led to speculation that this gene may be important for the human evolution of language. *FOXP2* expression in Neanderthals appears to have been absent or polymorphic (Maricic et al., 2013). In the human brain, *FOXP2* is expressed both in the ventral frontal lobe and in the basal ganglia (Spiteri et al., 2007). Consistent with these regional expressions, neuroimaging of persons with *FOXP2* mutations and language deficits shows decreased activity in cortical language areas, as well as in the basal ganglia (Vargha-Khadem, Gadian, Copp, & Mishkin, 2005). In other mammals, mutations of *FOXP2* are observed to affect neural plasticity generally, and the development of the basal ganglia specifically (Maricic et al., 2013). A consistent finding may be that when *FOXP2* mutations are created in mice, there is a decrement in dopamine levels. In addition, *FOXP2* variants are observed in mammals with echolocation skills, including cetaceans and bats, skills that may require unique capacities in neural plasticity, specifically in basal ganglia circuits for sensorimotor integration (Spiteri et al., 2007).

It is interesting to consider that the uniquely human mutations that enabled language function involved not only the highly elaborated cortex but also neurodevelopmental processes integral to dopaminergic modulation, to basal ganglia function, as well as to the activity in ventral frontolimbic networks. Through such vertically integrated neurodevelopmental mechanisms, the human capacity for routinized object cognition, such as language and mathematics, may be achieved through neurodevelopmental processes that are extended into adolescence, and are therefore vulnerable to the developmental dysregulation producing psychopathology.

Conclusion: Neurodevelopmental Motive Processes of Development and Psychopathology

The continuing progress in neuroscience is providing new insights into the biological mechanisms of neural development. In addition to genetic mechanisms, which can be cataloged

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now with remarkable breadth and precision, researchers are finding it increasingly necessary to understand epigenetic mechanisms, the self-regulatory capacities of the organism to achieve stable developmental trajectories, even in the presence of congenital aberrations and environmental challenges. A scientific explanation of psychopathology must move beyond crude generic notions, of stress causing epigenetic disorder, to explain the specific patterns of dysfunction of experience and behavior that are observed in developmental psychopathology.

In the search for a specific explanation, the fact that children exhibit disordered behavior in certain patterns, such as externalizing and internalizing, may be a clue to the dominant modes of neural as well as behavioral self-regulation that are normally adaptive but that become exaggerated in psychopathology. We have explored a theoretical analysis in which the developmental modes of externalizing and internalizing can be aligned with the unique neurophysiological cybernetics of the dorsal and ventral corticolimbic systems. In this analysis, we assume a straightforward identity of neural development with psychological development, such that the search for explanations of the neurodevelopmental mechanisms is clearly constrained by the obvious developmental patterns of normal personality and psychopathology.

The increasing understanding of neural plasticity in the distributed networks of the cortex, with its multiple subcortical control systems, is providing important theoretical tools for describing the neurodevelopmental process. We have pointed to the major neuromodulator systems of the dorsal and ventral corticolimbic divisions that provide unique modes of controlling neural activity in time. These may be described as motive neurodevelopmental processes, in that they provide motive control for both the neurodevelopmental organization of neural plasticity and the psychological domains of experience and behavior.

The human capacity for developing intelligence appears to have evolved to allow an extended period of neural plasticity, requiring an ongoing process of self-organization within the rich educational and cultural environments of human societies. This radical and extended plasticity may present vulnerabilities for varied developmental outcomes, including those of the major forms of psychopathology. At the same time, the study of critical periods in neural development points to the importance of constraints on neural plasticity, with developmental mechanisms that provide active termination of critical periods. These mechanisms for plasticity termination appear to be integral to normal maturation. Yet as we understand these mechanisms further, we may find that the process of maturation presents specific vulnerabilities for psychopathology that are as important as the inherent vulnerability of the extended human critical period of childhood neural plasticity.

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