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Review Article

Hyperbilirubinemia: Subcortical Mechanisms of Cognitive and Behavioral Dysfunction

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ABSTRACT

Although development of the full syndrome of kernicterus is relatively rare, neonatal jaundice continues to occur frequently. Controversy remains concerning whether or not infants with moderate elevations in bilirubin are at risk for neurodevelopmental disorders in later childhood. Sites of brain pathology associated with bilirubin neurotoxicity are identified and well established. Based on these regions of brain involvement, we apply neuroscientific principles of brain-behavior relationships to predict types of cognitive features that may accompany hyperbilirubinemia. We address a range of neurodevelopmental abnormalities that can arise as a function of elevated neonatal bilirubin levels affecting these brain regions, even in the absence of full kernicterus syndrome. Moreover, we explain the neuropathologic mechanisms that would drive these abnormalities. We thus attempt to establish a blueprint for future investigations of these conditions, to improve neurodevelopmental outcomes.

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Introduction

Kernicterus is a condition that occurs in neonates with hyperbilirubinemia. It is characterized by choreoathetoid cerebral palsy (with chorea, ballismus, tremor, and dystonia), sensorineural hearing loss, gaze abnormalities (with particular limitations in upward gaze), and dental enamel dysplasia. Improved emergent and intensive treatments have led to decreases in the most severe cases of bilirubin toxicity, so that reported cases of classic kernicterus have become relatively rare [1]. For example, in the United States, the frequency of this condition declined from approximately 5 per 100,000 in 1988 to 1.5 per 100,000 in 1994, and has remained constant since then [2,3]. In Nova Scotia, no cases of kernicterus were reported among 61,238 births between 1994 and 2000, after treatment guidelines for hyperbilirubinemia in term and late preterm infants were implemented [4]. Whether the prevalence of this condition is changing in other parts of the world remains unclear [5,6]. Current risk factors for developing kernicterus include early hospital discharge, increased prevalence of breastfeeding, and decreased awareness of the condition's pathologic signs, including difficulties in recognizing degrees of jaundice in certain racial populations [2]. Because kernicterus is now apparently relatively rare in developed countries, few longer-term follow-up studies have been undertaken, particularly in neonates who do not develop the full kernicterus syndrome.

According to Shapiro, although few infants develop this syndrome, neonatal jaundice remains prevalent in 60% of births [7]. Irreversible brain damage continues to occur in some of these children, although this damage may be preventable with a better understanding of the implications of jaundice and with the better treatments available. Furthermore, a historic, well established literature associates moderate elevations in bilirubin with neurodevelopmental problems in some infants who do not demonstrate the full kernicterus syndrome [8-11]. Recently, evidence that even moderate elevations in bilirubin can place infants at risk for cognitive, perceptual, motor, and

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auditory disorders has renewed interest in this topic. Elevated bilirubin in early infancy has been associated with later diagnoses of attention deficit hyperactivity disorder, autism spectrum disorder, central auditory processing disorders, general learning difficulties, and nonprogressive developmental delays [7,12-14]. Mildly abnormal general movements detected during the first 3 months of age stemming from moderate elevations in bilirubin levels during early infancy have been associated with attention problems, dysfunctional movements, and aggressive behavior at school age [14].

Cognition has been posited to develop from the motor system, and the ability to control thoughts and generate problem solving is posited as a reflection and outgrowth of what is first manifest as the ability to control movements and behavior [15,16]. Action control is movement control, and the control of action occurs through cognition. A rapidly developing literature that relates early movement abnormalities to later executive function deficits in childhood and adolescence raises significant clinical concerns about moderate levels of bilirubin in otherwise healthy infants, given the movement abnormalities associated with such elevations [17-22]. Accordingly, moderate elevations are no longer considered benign, and are instead considered potential contributors to later problems in attention, executive function, and learning [23]. A number of potentially confounding effects have become apparent in the study of elevated bilirubin, including prematurity, low birth weight, hemolysis, perinatal-neonatal complications, altered bilirubin-albumin binding, severity and duration of bilirubin exposure, and the individual vulnerability of the infant in terms of genetic, family, social, and educational predilections. However, cognitive deficits have been observed regardless of the cause of neonatal jaundice [13]. These conditions, which are classified as partial kernicterus syndromes, are often referred to as bilirubin-induced neurologic dysfunction or BIND.

Bilirubin-induced neurologic dysfunction, attention deficit hyperactivity disorder, and "intelligence quotient"

The clinical syndrome of bilirubin-induced neurologic dysfunction is controversial [24,25]. One recent study argued for a lack of association between early hyperbilirubinemia and a subsequent diagnosis of attention deficit disorder [26]. However, that study was seriously flawed because the data were collected only on children who had demonstrated moderately high total serum bilirubin levels within the first 30 days after birth and who had visited an outpatient clinic at least once at or after 3 years of age, with a diagnosis of attention deficit hyperactivity disorder. Attention deficit hyperactivity disorder, however, is a neurobehavioral disorder identified by a group of heterogeneous, behaviorally defined criteria [27]. Some aspects of nervous system functioning and cognition in developing children do not emerge until much later than the age of 3 years [28,29]. In fact, subtle manifestations of inattention may not be evident until a child passes through several grades of elementary school [30]. Children in the study who may have demonstrated characteristics of attention deficit hyperactivity disorder without meeting full behaviorally defined diagnostic criteria at that time would have been overlooked. Moreover, neuropsychologic tests were never administered to the children in that study to assess the specifics of their cognitive development, and therefore no information is available about specific features of their executive functioning or metacognitive skills. To our knowledge, that study is the only one that specifically contradicts an association between elevated bilirubin levels and a diagnosis of attention deficit hyperactivity disorder.

The issues associated with that study support a burgeoning awareness of the need for a dimensional approach to investigating attention deficit hyperactivity disorder and its associated features. The many problems inherent in the current overarching categoric approach taken by the Diagnostic and Statistical Manual, Fourth Edition are increasingly being recognized and explicated [31]. The current Diagnostic and Statistical Manual approach requires identifying a highly heterogeneous group of signs in order to render a diagnosis of attention deficit hyperactivity disorder [32-35]. The National Institutes of Health have instead emphasized the need to use a dimensional approach to investigate attention deficit hyperactivity disorder and most mental disorders [36-38]. The research domain criteria perspective they recommend includes using measureable behavior obtained through cognitive tests to identify specific features along with their neuroanatomic underpinnings. This research domain criteria approach is ideally suited for investigating the individual signs that may arise from bilirubin neurotoxicity, particularly because bilirubin manifests an affinity for attacking specific brain regions that are likely to lead to focal cognitive deficits.

There are limitations in other aspects of the literature that addresses the relationship between moderately elevated bilirubin levels in neonates and later developmental outcomes. Some studies have associated elevated bilirubin with developmental issues that are only vaguely characterized, such as "learning difficulties." Some studies portray elevated bilirubin in early infancy as unrelated to later childhood performance on intelligence quotient tests, but those studies have been criticized on methodological grounds [13,39,40]. At the same time, although the marginal differences reported in intelligence quotients between children with and without moderately elevated bilirubin in early infancy may be of some statistical significance, they are of limited practical significance. Intelligence quotients provide a very general "global index of functioning," as opposed to reflecting the quality of specific metacognitive capacities such as inhibition, working memory, planning skills, attention, and distractibility, all of which possess important adaptive implications.

Linking jaundice to cognition

The brain regions particularly vulnerable to hyperbilirubinemia are now well identified. Little attention has been given, however, to how abnormalities within these brain regions can contribute to specific cognitive and behavioral signs and pathologies, and neuropsychologic studies to illuminate the relevant brain-behavior relationships have not been performed. At the same time, given our current knowledge of brain-behavior relationships, we

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think it is possible to *predict* the types of cognitive and behavioral deficits that would occur, given the identification of these bilirubin-sensitive brain areas, their known interactions, and their functions. These predictions can be articulated on the basis of well established neuroscientific principles and a corresponding knowledge base derived from both experimental studies and clinical practice [4,41].

For example, frontal-basal ganglia interactions have been clearly implicated in inhibition/impulse control deficits, in executive function working memory processes that include decision-making, and in different subtypes of attention problems rooted in reward circuitry system dysfunction. Specific cognitive and behavioral functions are not addressed by intelligence quotient testing, and their measurement goes well beyond the scope of the broad intelligence quotient tests from which global "intelligence quotient" scores are derived. The basal ganglia comprise a critical hub in the connectivity profiles of these functions [42-47]. Damage to the basal ganglia as a consequence of bilirubin neurotoxicity would predict these types of higher-order cognitive and behavioral deficits because of the involvement of the globus pallidus interna and subthalamic nucleus. These areas, which are often affected by bilirubin toxicity, comprise essential network links within the direct and indirect pathways of the basal ganglia that govern these cognitive/behavioral systems.

This review will address the range of neurodevelopmental abnormalities that can arise as a function of elevated neonatal bilirubin levels affecting these brain regions, even in the absence of the full kernicterus syndrome. We will identify and characterize the predicted features, explain the neuropathologic mechanisms that theoretically drive these features, and establish hypotheses to direct future fruitful investigation.

Controversial issues in the measurement of elevated bilirubin levels

Subcortical areas and structures are selectively vulnerable to elevated levels of total serum bilirubin. It is generally accepted that total serum bilirubin levels greater than 335 μmol/L (19.6 mg/dL; a level defined as "moderate" at the 95th percentile ranking) should be avoided (see Johnson and Bhutani [13] for a comprehensive review of total serum bilirubin levels that is beyond the scope of this review). Controversy also arises as to whether *peak* total serum bilirubin levels in the neonate versus *duration* of bilirubin levels represents the relevant variable. Statistical analysis has suggested that the level of peak total serum bilirubin is most closely related to neurologic outcomes, whereas the duration of the total serum bilirubin elevation has not been regarded as the primary relevant factor (see Soorani-Lunsing et al. [12] for a review). To address how bilirubin levels should be measured or to explain the actual mechanisms of bilirubin neurotoxicity is beyond the scope of this paper (for a review, see Shapiro [7]). Preterm birth, very low birth weight, a possible genetic susceptibility to jaundice, bilirubin-albumin binding, and other birth complications all represent confounding variables when attempting to study the clinical spectrum of bilirubin-induced neurologic dysfunction systematically. However, our interest involves brain structure and function. Both the magnitude and the duration of elevated total serum bilirubin may exert a synergistic impact on neurodevelopmental pathologies.

Bilirubin neurotoxicity and brain structure

Neuropathologic and structural magnetic resonance imaging studies demonstrated remarkably selective patterns of injury to specific subregions of the basal ganglia in children with bilirubin encephalopathy [48]. Abnormalities have been consistently demonstrated at two primary sites of involvement within intermediate basal ganglia structures, i.e., the globus pallidus (both the internal and external segments) and the subthalamic nucleus. This finding is corroborated by autopsy results that confirm yellow staining [33-35], and by increased signal observed upon magnetic resonance imaging [49-51]. Other regions classically affected by bilirubin toxicity include the cerebellum (particularly the Purkinje cells), dentate nucleus, vermis, and fourth ventricle, as well as regions of the hippocampus [12,52]. Those studies also report abnormalities in various nuclei of the brainstem, with the greatest impact upon the cochlear, vestibular, and oculomotor nuclei. These brainstem abnormalities correlate strongly with the well-documented presence of central auditory processing disorders observed in cases of hyperbilirubinemia, and with the visual gaze and motor abnormalities observed in kernicterus [11,53-55].

Bilirubin neurotoxicity and the functions of the globus pallidus in prototypical frontal-basal ganglia circuits

Here we examine the possible cognitive and behavioral manifestations that are theoretically associated with these neuropathologic findings. First, we examine the role of the basal ganglia in generating neurodevelopmental pathology. Then we investigate the role of the cerebellum. Finally, we review the neuropsychologic pathology that may result from basal ganglia-cerebellar interactions.

Selective damage to the globus pallidus and the subthalamic nucleus is particularly relevant to neuropathology for several reasons. The pallidum plays a critical role within the cortico-striatal-pallidal-thalamic-cortical loop or circuit [56]. To review briefly, five parallel, functionally segregated circuits between the frontal cortex and the basal ganglia were originally identified. These were the skeletomotor, oculomotor, dorsolateral prefrontal, orbito-frontal, and medial/anterior cingulate circuits [57]. The basal ganglia receive afferents from nearly all cortical regions, including the temporal and parietal lobes, and they send segregated efferents back to the diverse thalamic nuclei that project to the cortical points of origin [58-61]. Therefore, the various frontal, inferotemporal, and parietal loops provide the basal ganglia with information from nearly all motor, sensory, and cognitive cortical brain regions. This system is topographically and functionally organized and segregated; circuit-related and regional specificity comprise important characteristics [62-65].

All of these circuits are connected to the striatum through direct and indirect pathways. The direct pathway projects from the striatum to the globus pallidus interna. The high spontaneous firing rate of the globus pallidus interna serves to inhibit the thalamus tonically, to prevent it

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from activating the cortex. Activation of the direct pathway through the striatum decreases globus pallidus interna inhibition and activates the thalamus, which releases the selected cognition or behavior. The indirect pathway involves inhibitory connections of the striatum to the globus pallidus externa. The globus pallidus externa contains inhibitory connections to the subthalamic nucleus/substantia nigra pars reticulata complex, which exhibits excitatory connections to the globus pallidus interna. Therefore, the activity of the indirect pathway causes the subthalamic nucleus to increase the tonic inhibitory activity of the globus pallidus interna, which suppresses behavior through thalamic inhibition. The direct pathway mediates cognitive and behavioral release, whereas the indirect pathway leads to cognitive, motivational, and behavioral suppression, dependent upon the circuit in question [66] (Fig 1).

It is therefore highly significant that hyperbilirubinemia affects the globus pallidus. Depending upon the regional area of involvement, attentional focus, concentration, response preparation, and response selection and inhibition may all be affected, which would become manifest as inattentiveness, distractibility, problems staying on task, and many of the behaviors that are characteristic of attention deficit and other neurodevelopmental disorders characterized by metacognitive/executive function deficits. We predict that these types of deficits would occur when the dorsolateral prefrontal circuit is affected. For example, Middleton observed that lesions confined to more rostral and dorsomedial regions of the globus pallidus interna produce the greatest cognitive deficits in patients [62]. The dorsolateral-striatal circuit projects to these regions of the globus pallidus interna, which inhibits dorsal-medial regions of the thalamus. This connectional profile predicts the specific cognitive involvement of the “executive functions” specified above, because decreased inhibition of the globus pallidus interna would increase thalamic “traffic,” thereby overactivating the cortex and leading to inattention and distractibility [67]. Even motor abnormalities, such as the choreoathetoid movements sometimes observed in

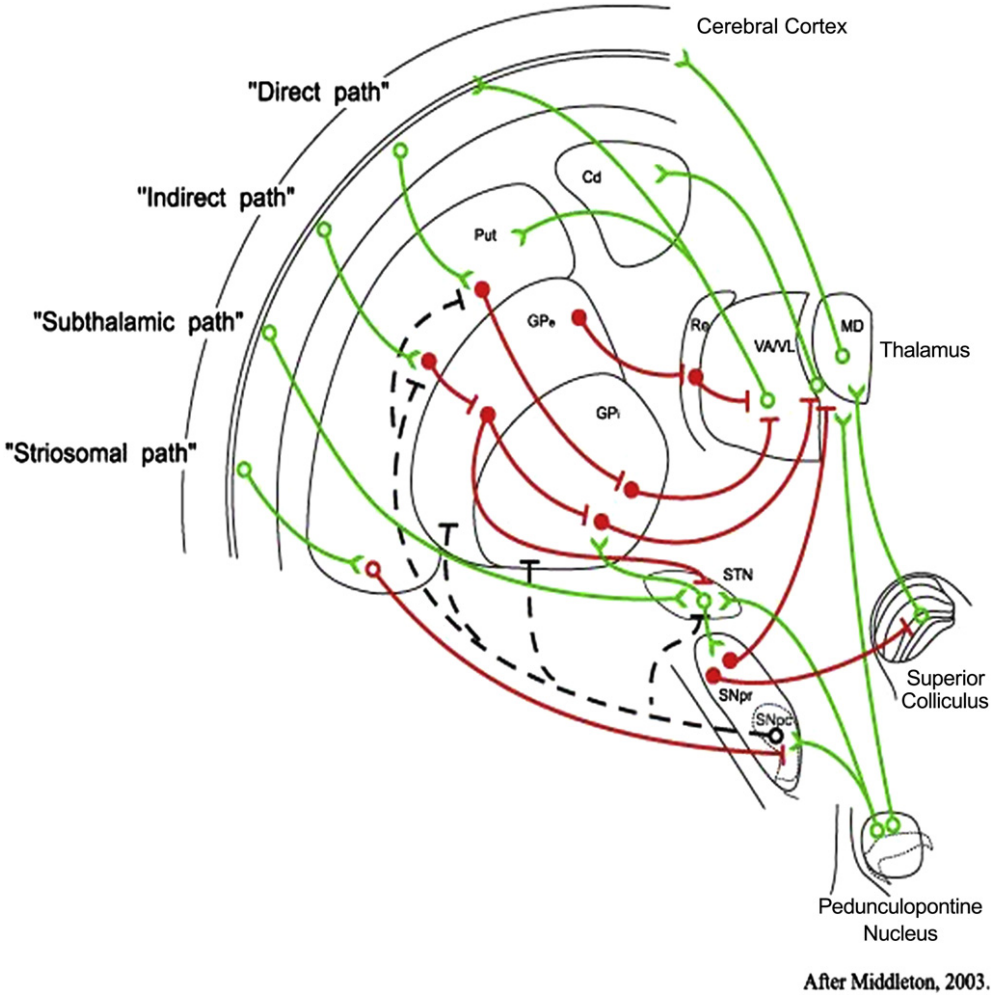

Figure 1. Basic cortico-basal ganglia circuitry. The organization of connections between different components of the basal ganglia and the cerebral cortex, the thalamus, and certain lower-level brainstem nuclei is depicted. Excitatory connections are presented in green. Inhibitory connections are presented in red. The broken line illustrates inputs from the SNpc to regions in the striatum, and these inputs can be either excitatory or inhibitory. Cd, caudate; GPe, globus pallidus externa; GPi, globus pallidus interna; MD, medial dorsal nucleus; Put, putamen; Re, reticular nuclei of the thalamus; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus. Not all projections from the caudate are illustrated. (Adapted with permission from Middleton [62].)

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children with attention deficit hyperactivity disorder, can be explained by pallidal inhibitory failures when posterior and ventrolateral regions of the globus pallidus interna (which project to motor areas of the cortex via the thalamus) are affected [68]. Therefore, both cognitive and motor deficits are predicted based upon the topographic organization of the globus pallidus [69,70].

Executive functions, self-control, and the globus pallidus

Given these affected aspects of function, pallidal involvement could further generate executive function deficits, including deficits in "working memory." Working memory is most simply defined as the ability to hold information cognitively "online" for a brief period of time sufficient for task completion. Working memory is foundational for a multitude of adaptive functions, including the capacity to "drive" behavior with voluntarily formed goals and intentions, and its integrity predicts performance in a wide variety of real-world cognitive tasks [71]. In the absence of working memory, a person is reduced to stimulus-bound types of behavior, and is unable to generate behavior dependent upon goal-directed thinking.

Working memory requires cortical storage of information within prefrontal-parietal lobe circuits, a circuitry that supports the ability to make informed decisions and choices based on previous experiences [72]. However, the mechanisms that maintain these multiple representations, ideas, and plans online, that manipulate these representations, that prevent the intrusion of distractions, and that update the contents of working memory are mediated by interactions between the cortex and the basal ganglia, and in particular, the globus pallidus [73]. Although working memory is represented bilaterally, evidence suggests that the left hemisphere makes a greater contribution to this function than the right hemisphere [70]. The direct and indirect pathways interact with the prefrontal cortex to perform various selective operations in a manner akin to that in which motor activity is selected and inhibited. These pathways select and inhibit cognitive activity in the same way they regulate motor activity. An overly simplistic analogy might refer to the way a "bouncer" selects and limits the people who are admitted to a nightclub [74].

Whereas prefrontal-cortical connections maintain information "online," basal ganglia-cortical interactions through the globus pallidus interna and globus pallidus externa prevent distractions from intruding. In essence, the globus pallidus, through interactions with thalamic nuclei, "let in" the desired information and "keep out" the distracting information. In this manner, working memory can be characterized as arising from a division of labor between cortical information maintenance and basal ganglia informational gating and manipulation. Bilirubin toxicity-related impairment within dorsal regions of the globus pallidus affects these working memory functions, which become increasingly critical to a child's academic success as he or she progresses through school [75,76]. Chatham et al. demonstrated that children do not even begin to make the slow and gradual transition from contextually appropriate reactive behavior to behavior that is self-directed by working memory processes until approximately 8 years of age [77]. Accordingly, working memory deficits are likely to go undetected in very young children, and may not be evident or identifiable until a child advances to approximately the fifth grade [78,79]. This developmental observation has been well documented, and was described in detail by Denckla and Reader [30].

Neurotoxicity and the subthalamic nucleus hyperdirect pathway

Certain regions of the motor, premotor, and supplementary motor cortices and frontal eye fields bypass the direct and indirect pathways of the striatum and project directly to the subthalamic nucleus [80]. These direct projections have been called the subthalamic or hyperdirect pathway. Because this pathway excites the subthalamic nucleus, its activation results in increased activity in the globus pallidus interna. This increased activity further stimulates globus pallidus interna tonic inhibition over the thalamus, which suppresses behavior. The hyperdirect pathway functions 2-2.5 times faster than the indirect pathway because it contains fewer synapses. Its activation represents the quickest way to terminate a behavior in the process of execution. In this manner, the hyperdirect pathway plays a critical role in preventing "premature responding" and facilitating impulse control [81].

Bilirubin neurotoxicity often targets the subthalamic nucleus. Failure of the subthalamic nucleus to activate the globus pallidus interna would be expressed in the impulsive and even stimulus-bound behavior often characteristic of children with attention deficit hyperactivity disorder and other neurodevelopmental disorders associated with impaired impulse control. Aron and Poldrack observed a fundamental role for the subthalamic nucleus in response inhibition, identifying this region as a primary candidate for investigation in impulse-control disorders [82]. Frank et al. also demonstrated that deactivation of the subthalamic nucleus leads to deficits in impulse control [83]. Impulse control problems characteristic of neurodevelopmental disorders and driven by anomalous pathology within the subthalamic nucleus may be preventable through the appropriate detection and early treatment of bilirubin neurotoxicity.

Neurotoxicity in basal ganglia integrative networks

The prototypical basal ganglia circuits (as already described) were initially characterized as highly segregated, with each circuit subserving a discrete functional behavior [57,84], and each following the connectional pattern of the direct and indirect pathways. Although all circuits operate as parallel processes, it makes both intuitive and logical sense that discrete, specific behaviors arise from segregated operations within this pattern of parallel circuitry activation. This pattern of activation explains how attention and action/behavioral selection become highly focused and maintained. At the same time that segregated circuitry supports specific, focused attention selection and behavioral activation, developing appropriate responses to events in "real life" requires that we continually update, change, and adjust behaviors "online" as novel information from either the external or internal "environments" becomes available [85,86].

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Responding with smoothly executed, goal-directed behavior requires coordination and interaction between limbic/emotional/motivational and cognitive/motor circuitries. Unfortunately, the parallel and segregated processing of functional information through these cortical-basal ganglia circuits does not explain this coordination. In fact, solely emphasizing the patterns of segregated circuitries interferes with an understanding of how information flows between circuits for the adaptive purpose of generating new, or changing previously learned, behaviors or actions. Adapting to a changing environment requires ongoing updating and learning, so that parallel, segregated circuits of the basal ganglia have to be coordinated to generate and execute appropriate goal-directed behaviors. An informational flow *between* circuits is needed if previously learned actions are to be adapted and new behaviors are to be developed [87,88]. In pediatric populations, learning new behaviors marks the unfolding of neurodevelopmental processes. Therefore, understanding how cortico-basal ganglia circuits interact is critical if we are to understand general adaptation, and an understanding of how these interactions may be affected by neurotoxicity is equally critical [89].

Basal ganglia circuits appear to involve four integrative networks [87]. Whereas cortico-striatal pathways are primarily characterized by focal, circumscribed, and topographically organized projections, some overlap is evident between the terminal fields from these different functional regions, and in specific regions, focal projections from cognitive and reward-related prefrontal areas converge. Cortical cognitive and motor control areas also converge at specific regions within the striatum [87,90]. Furthermore, although the globus pallidus interna is also topographically organized according to functional domains, information integration through the pallidum occurs via convergence at the borders between functional domains. In addition, within the external segment of the globus pallidus, projection fibers extend well into other nearby functional domains through the domain border areas [87]. A midbrain striato-nigro-striatal projection system has also been identified that includes reciprocal connections with cognitive, limbic/motivational, and motor regions of the striatum. These connections provide a potential mechanism for the integration of motivation and cognition to influence motor decision-making processes in response to environmental cues. Lastly, the thalamo-cortical pathway is not a simple "relay station" to permit the thalamus to activate the cortex. Instead, the thalamus contains additional, nonreciprocal connections that project to nearly all cortical layers, in addition to those parallel and segregated regions from which the cortico-striatal-thalamo-cortico loop originates.

Therefore, cognitive/associative, motivational/reward, and motor control functions are not discretely, distinctly, or completely segregated within cortico-striatal networks. In addition to the now well-recognized parallel and segregated circuits, specific integrative networks function in concert with parallel circuitry. These networks allow behaviors to be focused, maintained, modified, and changed, and they allow an organism to learn new behaviors that permit it to act in its own best interest. Because the internal and external segments of the globus pallidus comprise the primary sites of pathology in bilirubin toxicity, a vast potential exists for information integration to be interrupted by elevated bilirubin. This condition would exert a profound impact on the information integration functions that allow existing behaviors to be modified and new behaviors to be learned. Involvement within this system would theoretically affect learning new cognitive sequences or ideas, such as arithmetic skills [91]. It could affect the acquisition of printing and cursive writing skills, and the ability to perform on drawing tasks. Practical procedures that require automation, such as dressing, using buttons, and tying shoelaces, would likely also be affected. The ability to benefit from the reward inherent in successful task participation could be affected. These are but a few pertinent examples. The implications are profound when one considers that basal ganglia dysfunction underlies the procedural and instrumental (reward-based) learning difficulties characteristic of many children with neurodevelopmental disorders [92-95].

Bilirubin neurotoxicity and the cerebellum

Although regions of the basal ganglia appear to be the most affected by hyperbilirubinemia, the lesser involvement of cerebellar structures should not be overlooked. This involvement is implied by the segregated cerebro-cerebellar circuitry profiles described by Schmahmann and Pandya [96], and by the fact that the basal ganglia and cerebellum communicate with each other. Cerebro-cerebellar "loops" originate in the cortex, and then project to the pons, to the cerebellar infrastructure through the mossy fiber input system, to the deep cerebellar nuclei, and then back to the cerebral cortex via the thalamus [97-101]. Reciprocal connections also extend from the subthalamic nucleus (a primary inhibitory nucleus of the basal ganglia) to sensorimotor, associative, and limbic regions of the cerebellum. The cerebellum projects back to the neocortex and to the striatum, which is the basal ganglia's primary source of sensory input [102,103]. Understanding circuitries between the basal ganglia and cerebellum is critical if the presentations of signs that characterize developmental disorders are to be understood, because both the subthalamic nucleus and the cerebellum are implicated in abnormal pediatric development and can be affected by bilirubin neurotoxicity.

Manto and Jissendi recently demonstrated the role of the cerebellum in linking normal development, developmental disorders, and motor learning [104]. Impairment in the cerebro-cerebellar circuitry profile also often results in cerebellar cognitive affective syndrome [105]. This condition is characterized by disturbances in executive functioning, working memory impairment, language deficits, problems in visuospatial organization, and visuomotor deficits. This deficit pattern is often observed in children with developmental coordination disorder, a condition in which both the basal ganglia and cerebellum are affected [106-110]. When the vermis or "limbic cerebellum" is involved, personality characteristics such as irritability, emotional lability, and even autistic-like cognitive and behavioral features have been reported [111]. A further question concerns the increased incidence of autism spectrum disorders when the cerebellum is affected by hyperbilirubinemia, given that the cerebellum is the most commonly observed site of abnormality within that patient population [13]. Because cerebro-cerebellar connections are essential to normal development and because such an

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intimate relationship exists between motor development and cognitive development and between the cerebellum and the prefrontal cortex, young children with cerebellar problems often demonstrate persistent deficits [104,112]. When cerebro-cerebellar feedforward and feedback loops are affected, the young, developing brain does not appear to reorganize itself to compensate [113-115].

Basal ganglia and cerebellar interactions

Stimulation within the subthalamic nucleus of the basal ganglia inhibits or "stops" behavior, and is thus implicated in perceptual and activity selection processes [81,83]. Basal ganglia-cerebellar and cerebro-cerebellar circuitry may interact cooperatively, competitively, or independently (for a comprehensive review of these circuitry systems, their interactions, and resultant signs, see Koziol et al. [116]). Problematic interactions stemming from bilirubin-induced neurologic dysfunction may generate hyposensory and hypersensory sensitivities that characterize what occupational therapists describe as sensory processing and sensory modulation disorders. The cerebellum mediates the force of sensory input and motor output [117]. Whereas impairment of the subthalamic nucleus results in inhibitory failures that lead a child to notice, be attracted to, or be distracted or bothered by stimuli to which he or she would ordinarily habituate, aberrant activity of the subthalamic nucleus/cerebellar projection system could lead to *abnormal dentate nucleus activity*, which would dysregulate sensation and behavior [116]. Problems might range from hyporesponsiveness or hyperresponsiveness to sensory stimuli to temper outbursts and emotional management problems, dependent on how focal or extensive the area of circuitry involvement might be. The sensory profile, used by occupational therapists to assist in identifying these problematic behaviors, is replete with items that reflect hypermetric and hypometric dimensions of experience in all sensory modalities [118]. Sensory processing disorders occur more frequently in children with histories of preterm delivery, low birth weight, and jaundice. This triad of clinical problems confounds our understanding of these conditions.

Attention deficit hyperactivity disorder is one of the most common and well known neurodevelopmental disorders, and both the basal ganglia and the cerebellum participate in generating this condition [119-121]. The typical problems associated with attention deficit hyperactivity disorder (e.g., acting too quickly or without executive control) imply deficits within frontal-striatal-pallidal-thalamo-cortical circuitry systems [23,122-128] and cerebro-cerebellar circuitry [129-132]. In a study by Mackie et al. [133], a group with attention deficit hyperactivity disorder demonstrated significantly smaller volume of the vermis, and those subjects with the smallest volumes of the cerebellar hemisphere demonstrated the worst therapeutic outcomes. All of these brain regions have been reported to be affected by hyperbilirubinemia.

Discussion

This review considers the controversy associated with a spectrum of disorders often referred to as bilirubin-induced neurologic dysfunction. Although the effects of kernicterus syndrome have been studied extensively, limited attention has been paid to children with moderate levels of hyperbilirubinemia. Some studies fail to detect a relationship between moderate elevations in bilirubin levels and pathologic neurodevelopmental, childhood, adolescent, or adult outcomes. A relationship seems to exist between elevated bilirubin levels and an increased incidence of auditory processing disorders [13]. As reviewed by McCandless [134], conclusions of studies that evaluated the relationship between elevated bilirubin levels and intelligence as measured by intelligence quotient tests are equivocal. Only vaguely defined cognitive, learning, emotional, and behavioral deficits are sometimes described [134]. Intelligence quotient tests measure global levels of ability that typically follow the normal distribution of a bell-shaped curve. Most of the specific, sensitive cognitive functions that would predictably be affected by bilirubin neurotoxicity are simply not identified by intelligence quotient tests [135]. Therefore, we do not think that global "intelligence quotient" is the appropriate variable for investigation when studying the possible effects of hyperbilirubinemia. Similarly, the review by McCandless [134] and a study by Newman and Klebanoff [39] minimized the significance of seemingly "minor" or "trivial" motor abnormalities that appear to resolve spontaneously in children with moderate hyperbilirubinemia. However, even minor movement abnormalities that remit can be significant within a neurodevelopmental framework. A rapidly expanding literature views all movement as purposeful and essential to the subsequent development of higher-level, executive order control functions [136-138]. The reader is referred to Koziol et al. [112] for a summary of this literature.

At the same time, neuropathologic studies and certain types of neuroimaging studies have consistently identified selective sites of pathology in children with hyperbilirubinemia. Pathology has repeatedly been identified in highly specific regions of the basal ganglia and within certain regions of the cerebellum. On the basis of these findings, we predict several specific types of cognitive, affective, sensorimotor, and behavioral problems that should be generated by deficits within these areas. These predictions, or hypotheses, are based upon known, accepted neuroscientific principles of brain-behavior relationships. These predictions are testable and warrant further investigation.

Future studies need to be longitudinal in nature, while examining several variables. First, bilirubin levels need to be measured, and the duration of jaundice should be monitored and recorded. Although our review indicates that peak bilirubin levels may comprise the more important risk factor for kernicterus in relation to the development of severe cognitive impairment, the duration of elevated bilirubin levels may well be related to development of deficits in sensitive cognitive functions that develop relatively slowly during the course of childhood and early adolescence. Equally important, rather than correlating elevation and duration of bilirubin levels with a heterogeneous categorical diagnosis such as attention deficit disorder, we recommend using research domain criteria, as advocated by the National Institutes of Health. For example, although any given individual may not meet the range of behaviorally defined, observational criteria needed for a formal diagnosis of attention deficit

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hyperactivity disorder, the individual may still manifest significant impairment in highly specific cognitive functions. Similarly, we do not advocate investigations that simply apply a broad-based battery of cognitive and neuropsychologic tests yielding aggregate scores. Index scores summarize the variables of interest into a composite score that confounds and obscures examination of the specific functions in question. Individual cognitive measures sensitive to specific areas of function should be used instead.

The cognitive functions that warrant investigation include those that are highly specific and dependent upon cortico-basal ganglia and cerebro-cerebellar functional connectivity profiles. Although these cognitive processes are frequently referred to with the overarching terminology of "executive functions," the discrete functions that define executive control need to be specified and individually measured with clinical and research paradigms that are already used within the clinical and experimental literature. The use of these paradigms would ensure that for each function measured, the same brain regions and networks would be elicited, as established by previous studies of the particular function, so that the results would be directly comparable. For example, the Sternberg working memory paradigm has been used to "map" the complex brain network often affected in attention deficit hyperactivity disorder [45]. Stevens et al. used a highly specific yet brief Go/No-Go paradigm that identified a hierarchically organized, three-component response inhibition circuitry that has been interpreted as essential to facilitating impulse control, limiting distractibility, and accessing working memory function/higher-order cognitive control processes [43,44]. Moreover, Frank et al. used a probabilistic category learning task that identified the cortico-basal ganglia networks involved in reward circuitry that are critical for understanding motivation and preferences for positive or negative reward [139-141]. All of these paradigms have been successfully applied to the investigation of critical, specific cognitive functions while adhering to the specificity of research domain criteria. (The interested reader is referred to Koziol and Stevens [47] for further discussion of why research domain criteria approaches are necessary, and for examples of how this investigative methodology can be applied to specific areas of cognition and behavior.) Motor abnormalities, even when they initially appear to be relatively minor, have been investigated and identified by applying the Physical and Neurological Examination for Soft Signs [142,143]. This motor examination has proven useful in identifying patterns of motor abnormality in a variety of diagnostic conditions [144,145]. All of these procedures should be applied to the study of moderate elevations in bilirubin levels, and can also be readily applied to practical clinical examinations.

We have laid a foundation for the organization and implementation of studies to confirm or reject our predictions and hypotheses. We consider this is a critical first step in defining the issues that must be addressed to clarify the relationship between hyperbilirubinemia and developmental disorders, to determine the value of treatments for potentially preventable developmental conditions in children. Babies born preterm, very preterm, and with low birth weight are perhaps at the greatest risk for developing jaundice. Studies also demonstrate that very preterm births and especially low birth weights constitute significant risk factors for poor outcomes among adolescents, young adults, and adults [146,147]. However, these studies [146,147] did not focus specifically on elevated bilirubin as an area of interest. Scientific technologies that allow these issues to be parsed may not be available for quite some time. We have nevertheless established a "blueprint" for the systematic investigation of possible impairment in specific cognitive processes. We hope that this approach will prove fruitful in helping the pediatric population we serve.

Conclusions

We have described the condition known as kernicterus and the related spectrum of bilirubin-induced neurologic dysfunction. Based on the well established sites of pathology observed in kernicterus, we have developed a series of hypotheses about the predicted brain-behavior relationships that should be affected as a manifestation of abnormalities within these regions of brain involvement for children with bilirubin-induced neurologic dysfunction. Instead of supporting global approaches to the assessment of cognition and a categorical approach to diagnosis, we have emphasized a systematic investigative method that focuses upon the evaluation of specific features. This method allows for the symptomatic treatment of identified deficits, which should prove useful among children with vaguely defined neurodevelopmental disorders that may be etiologically related to moderate elevations in hyperbilirubinemia.

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