Published in final edited form as:

Curr Diab Rep. 2014 October ; 14(10): 533. doi:10.1007/s11892-014-0533-x.

Neurocognitive Outcomes in Pediatric Diabetes: a Developmental Perspective

David D. Schwartz,

Section of Psychology, Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA. Psychology Service, Texas Children's Hospital, 6701 Fannin Street CC 1630, Houston, TX 77030-2399, USA

Rachel Wasserman,

Section of Psychology, Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA. Psychology Service, Texas Children's Hospital, 6701 Fannin Street CC 1630, Houston, TX 77030-2399, USA

Priscilla W. Powell, and

Section of Psychology, Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA. Psychology Service, Texas Children's Hospital, 6701 Fannin Street CC 1630, Houston, TX 77030-2399, USA

Marni E. Axelrad

Section of Psychology, Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA. Psychology Service, Texas Children's Hospital, 6701 Fannin Street CC 1630, Houston, TX 77030-2399, USA

David D. Schwartz: ddschwar@bcm.edu

Abstract

The impact of diabetes on the developing brain is well-accepted. Effects on neurocognitive functioning are moderate but have larger functional implications, especially when considered through a developmental lens. Pathophysiological factors such as severe hypoglycemia and chronic hyperglycemia can alter developmental trajectories in early childhood and perhaps at later periods. In this paper, we selectively review neurocognitive outcomes in pediatric diabetes (largely type 1), integrating recent research from developmental neuroscience and neuroimaging. We examine the effects of diabetes at different stages and place findings within a neurodevelopmental diathesis/stress framework. Early-onset diabetes is associated with specific effects on memory and more global cognitive late-effects, but less is known about cognitive outcomes of diabetes in later childhood and in adolescence, a time of increased neurobehavioral vulnerability that has received relatively limited empirical attention. Studies are also needed to better elucidate risk and protective factors that may moderate neurodevelopmental outcomes in youth with diabetes.

Correspondence to: David D. Schwartz, ddschwar@bcm.edu.

Conflict of Interest David D. Schwartz, Rachel Wasserman, Priscilla W. Powell, and Marni E. Axelrad declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Type 1 diabetes; Cognitive; Neurocognitive; Developmental; Neurodevelopment; Children; Adolescents; Pediatric; Review

Introduction

In recent years, there has been an explosion of research examining the effects of diabetes on the central nervous system (CNS) and neurocognitive functioning. In part, this reflects new possibilities opened up by advances in neuroimaging, such as the use of diffusion tensor imaging (DTI) to visualize white-matter tracts, but there is also growing recognition of the importance of diabetes-related cognitive deficits to functional outcomes and health-related quality of life. Cognitive outcomes of adults with type 2 diabetes are understood to be a critical public health issue. In contrast, we are only just beginning to grasp the implications of the effect of diabetes-related cognitive complications on pediatric populations. It is well-known that cognitive effects of pediatric diabetes (primarily type 1; T1D) are relatively small, with small to medium effect sizes compared to non-diabetic controls, and test scores that largely fall within the average range. However, small effects can have a large impact when considered at the population level, especially as the prevalence of pediatric diabetes increases.

It is generally agreed that the cognitive effects of diabetes depend in large measure on the developmental timing of disease-related events. This is an unavoidable outcome of normal brain development, which undergoes different patterns of maturation in different regions. In general, areas undergoing development at the time of disruption are more vulnerable than areas that have already matured or mature later on [1]. Brain development proceeds in a back-to-front fashion, with more phylogenetically older structures involved in sensorimotor function (occipital lobe, parietal lobe) maturing first, followed by higher-order association cortices, and lastly by the frontal lobes. Gray matter increases in volume throughout childhood and then begins to decline in adolescence, due to neuronal pruning as well as increasing myelination. In contrast, white matter increases into early mid-adulthood, and functional networks develop and become more specialized over time [2]. Areas that undergo protracted periods of development, such as the hippocampus, frontal lobes, and white-matter tracts, are more vulnerable to stress and insult [3].

In a seminal paper, Desrocher and Rovet [4] proposed a neurodevelopmental model of T1D based on a review of the literature at that time, placing neurocognitive outcomes in a framework tied to the development of the CNS. According to the model, severe hypoglycemia in early childhood is differentially associated with deficits in motor and visual-spatial functioning and, somewhat later, in memory and attention. The effects of chronic hyperglycemia were proposed to be largely confined to adolescence and to frontal brain networks that undergo rapid maturation post-puberty, with specific effects on the development of executive functioning. One goal of the present paper is to update this model based on more contemporary research.

An implication of the neurodevelopmental model is that the CNS will be particularly sensitive to insult during periods of rapid maturation. Ryan [5, 6] and Biessels et al. [7] suggested two “crucial periods” of CNS vulnerability: early childhood (the first 5–7 years of life) and senescence (>60 years). They suggested that cognitive decrements primarily occur during these two periods, with the time in between representing “non-crucial periods” of cognitive stability (except where there are microvascular or macrovascular complications). Later childhood and adolescence were not specified in this model, but the implication seems to be that they are also largely seen as non-crucial periods.

In the sections that follow, we review recent data as it pertains to an updated neurodevelopmental model, with a focus on children and youth with T1D and different periods of potential neurocognitive vulnerability. This is not meant to be a systematic review but a consideration and interpretation of recent research within a developmentally oriented conceptual framework. First, we discuss two important concepts related to the model—late-effects and diathesis/stress—and their evidence base in the T1D literature. Next, we review current evidence for differential effects of diabetes at different ages. As will be seen, the majority of data pertain to the effects of early onset of disease (EOD); much less research has explicitly examined effects at later ages. A second purpose of this review is to sketch out areas in which further research into the neurodevelopmental model is needed.

Neurodevelopmental Framework

Cognitive Late Effects

Many children with chronic illness experience acute injury to the CNS with effects on cognitive function that are not apparent until later (often years later) in the disease course, a phenomenon termed “cognitive late-effects” [8, 9]. Injury may result from factors related to the disease (e.g., stroke) or its treatment (e.g., cranial radiation therapy for cancer). Cognitive late-effects have been documented in multiple illnesses including pediatric cancer, sickle cell disease, HIV [8], congenital heart disease, cystic fibrosis, rheumatologic disorders [10], and head injury [11]. Late-effects might also provide a way to understand some of the cognitive impact of pediatric diabetes.

Cognitive late-effects are understood to arise from disruption of the *development* of CNS structures or functions. In children with chronic illness, disease and its treatment typically affect structures and abilities that have not yet reached full maturation, but leave already developed areas largely intact [8, 9]. Neurodevelopmental models therefore predict that earlier age of disease onset will be associated with more global and severe disruptions of development, whereas the impact of later onset would be limited to later-developing brain areas (e.g., frontal lobes) [4]. As discussed later in this paper, these predictions find some support in the pediatric diabetes literature. Candidate events that may be associated with cognitive late-effects in diabetes include peri-onset dysglycemia, diabetic ketoacidosis (DKA), and severe hypoglycemia.

A commonly reported mechanism underlying late-effects in many chronic illnesses is white-matter damage, which is associated with slower processing speed that affects children’s learning trajectories and, ultimately, IQ (e.g., [8, 9, 12, 13]). A similar process may be

operant in T1D. Diabetes-related dysglycemia has long been known to affect myelination [14], and the most commonly reported cognitive deficits in T1D are reduced psychomotor speed, attention, and executive functioning [15–17], with later-emerging decrements in IQ [18, 19]. To date, much of the research on cognition in T1D has focused on the effects of specific pathophysiological mechanisms on specific brain structures, perhaps to the neglect of a more general disruption in white matter and information processing.

Diathesis/Stress

Diathesis/stress models provide an additional framework for understanding neurodevelopmental effects of diabetes. The term “diathesis” refers to a constitutional disposition or predisposition—a preexisting vulnerability—to the development of a disorder or complication in response to some precipitating factor (the stressor) [20]. Vulnerability can arise from genetic and physical factors, early environmental exposures, and early insult. A central implication is that some individuals are more vulnerable to the negative effects of stress or insult than others and that it will take a lower level of stress (or severity of injury) to produce a pathological outcome in a person with high (versus low) vulnerability.

In two influential papers, Ryan [5, 6] proposed that dysglycemic events around the time of diabetes diagnosis might increase the vulnerability of brain tissue to future dysglycemia. Individuals often experience prolonged untreated hyperglycemia in the peri-onset period. Rising blood glucose concentrations can temporarily increase blood-brain-barrier permeability, allowing glucose to flood the brain and potentially affecting neuronal integrity [6]. Another possible diathesis is DKA, which occurs in approximately 30–40 % of children at diagnosis [21] and is associated with subclinical edema in at least half of all cases [22]. However, the long-term impact of these acute changes on cognitive function is largely unknown.

Ryan suggested that peri-onset metabolic fluctuations could increase vulnerability of the CNS to the cognitive impact of neuroglycopenia. One study that directly tested this hypothesis [23] found no relation between early exposure to hyperglycemia, later severe hypoglycemic events, and performance on tests of memory and spatial abilities. However, it remains plausible that early hyperglycemic exposure may increase vulnerability to events such as DKA [24•] or to the long-term effects of chronic hyperglycemia and hyperglycemia-induced oxidative stress [25••, 26]. Consistent with this possibility, DTI studies have begun to show subtle changes in cerebral white-matter integrity in children with brief diabetes duration, prior to any measurable volume loss [27]. These changes are associated with prior hyperglycemic exposure [28] and may provide a leading indicator of axonal vulnerability predictive of subsequent white-matter loss [26, 29••]. Another recent DTI study [30••] found a significant association between white-matter structure and A1c at study baseline, but not with a “lifetime” index of A1c, suggesting insult was more likely related to acute (versus chronic) effects of hyperglycemia nearer the time of diagnosis. Our group found a high incidence of impairment in bilateral fine-motor speed, visuomotor integration, and phonemic fluency in children within days of T1D diagnosis [31]. While we do not know whether these acute deficits resolve with a return to euglycemia, impairments in motor speed and working memory were associated with diabetes outcomes over 1 year post-diagnosis, which suggests

that acute cognitive dysfunction may be an early marker of neurobehavioral vulnerability. However, other studies have generally found that reliable group differences (T1D versus non-T1D) in cognitive function are not evident until 2 years after onset [18, 32]. If peri-onset effects do influence cognitive functioning, this pattern of delayed emergence supports a vulnerability model rather than a direct (immediate) effect of peri-onset dysglycemia on CNS. Risk for long-term cognitive complications may be especially likely in children with acute cognitive dysfunction at diagnosis who go on to experience chronic glycemic dysregulation.

Genetic and Environmental Risk Factors

Genetics and early environmental factors are likely important contributors to the diathesis for cognitive effects of T1D, although these are relatively understudied areas. A few studies have examined the potential role of genetic polymorphisms in apolipoprotein E (APOE) on diabetes-related cognitive outcomes, as APOE alleles are associated with increased risk for dementia and cognitive dysfunction in individuals with T2D [33]. One cross-sectional study found an association between APOE alleles and cognitive dysfunction in adult females with T1D [34], but this finding was not replicated in a much larger study examining follow-up data from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study [35]. Variants of angiotensin-converting enzyme genes were also unassociated with cognitive outcomes in this cohort.

Polymorphisms in glutathione *S*-transferase (GST) are another promising target for investigation. GSTs play an important protective role against oxidative stress [36] and are associated with attention problems in children treated for leukemia [37]. Moreover, impaired glutathione metabolism is a common feature of diabetes [38]. A recent study of adults with T1D found significant associations between *GSTM1* polymorphic deletion and risk for retinopathy in adults with T1D [39], and other studies link retinopathy to risk for cognitive decline [40].

Early life stress may be another important contributor to cognitive vulnerability in T1D. There is an extensive literature documenting the effects of high or chronic early stress on the developing CNS, especially the hippocampus and frontal lobes [3], areas known to be more vulnerable in T1D. Unfortunately, the incidence of traumatic early life stress is disturbingly high, especially among impoverished and minority children; and factors such as poverty and family conflict also have detrimental effects on brain development [41]. To complicate matters, stress and diabetes likely interact in their effects on brain development, and stress typically elevates blood sugars, increasing hyperglycemic exposure. However, we know of no research to date examining early life stress, deprivation, and neurocognitive vulnerability in T1D.

Effects of Diabetes During Different Developmental Periods

Early Childhood

Over 50 years ago, it was discovered that children with early onset of diabetes (EOD) were more likely to develop neurocognitive deficits [42]. Much subsequent research has been devoted to understanding this early-onset effect. The first few years of life are a period of

rapid and dramatic neurodevelopment, and the developing brain is especially dependent on having an uninterrupted supply of glucose [43]. Thus, it has been suggested that the CNS may be especially vulnerable to glycemic fluctuations at this stage [44].

Other factors contribute to the increased risk associated with EOD. According to a neurodevelopmental late-effects account, younger age will be associated with more significant and global deficits given that fewer brain areas and functions will have matured prior to diabetes onset. Earlier onset will also translate into a greater overlap of diabetes (and diabetes-related dysglycemia) with developmentally sensitive periods. In this respect, earlier onset is often confounded with duration in many studies, although this problem can be mitigated by careful designs that control for duration and glycemic events [23]. Very young children are also less able to recognize and report symptoms of hypoglycemia, making them especially prone to severe hypoglycemic events that can affect the CNS, and incidence of DKA at diagnosis is significantly higher in children 0–4 years of age [21]. Of course, these possibilities are not mutually exclusive and probably interact for many children with diabetes.

In a comprehensive meta-analysis of early-onset effects, Gaudieri et al. [16] found reduced memory, attention/ executive functioning, and crystallized IQ in children with EOD compared to controls without diabetes (effect sizes generally -0.3 to -0.5), with attenuated effects compared to children with later onset (effect sizes -0.2 to -0.3). These findings are in line with longitudinal data [45•, 46]. Surprisingly, another meta-analysis [17] found no significant effects of EOD. There was a medium effect on performance IQ (PIQ), but it did not reach significance ($d=-0.38$, $p=0.08$). The reason for the discrepancy between these meta-analyses is unclear.

In general, the largest effects of EOD (compared to later onset) have been found in learning and memory, despite the fact that this is the one cognitive domain where T1D/non-T1D group differences are *not* evident [16]. This suggests that memory and the brain regions that subserve it (hippocampus, medial temporal lobe) are differentially vulnerable in early childhood. Recent neuroimaging studies support this view [25•, 47]. Severe hypoglycemia is a likely mechanism [25•], as it is associated with neuronal damage in the hippocampus [48] and with learning and memory [49•, 50]. A recent study by Hershey et al. [51] found abnormal enlargement of the hippocampus in children with T1D associated with severe hypoglycemic episodes. Other work suggests that children with EOD are at higher risk for memory impairment secondary to DKA [26], which is associated with changes in the thalamus [28, 46], another structure involved in memory [52].

Diffuse cerebral white-matter changes on DTI have also been reported in EOD [30•], with correlations evident between A1c, fractional anisotropy (a measure of white-matter density, myelination, and coherence), and IQ. In other illness groups, it has been demonstrated that attention problems and slower processing speed mediate the relationship between white-matter damage and subsequent changes in IQ [53]. A similar relation may be operating in children with EOD of diabetes, who also have a higher incidence of attention problems [14, 45•]. These changes might be mediated by chronic hyperglycemia. Differences in cognitive

abilities, motor speed, and receptive language have all been noted in children with EOD and poor glycemic control [54].

In summary, EOD is associated with changes in the hippocampus, medial temporal lobe, and thalamus, structures associated with learning and memory, and with whole brain white matter. Consistent with the neurodevelopmental model, cognitive effects are relatively global, encompassing attention, executive functioning, language, and IQ in addition to memory, with larger effects evident in areas (e.g., memory) undergoing rapid development at the time of diabetes onset. The effects of severe hypoglycemia on the CNS may largely be restricted to this developmental period.

Later Childhood

Effects of diabetes on the CNS and cognitive function in later childhood (roughly, ages 7–12) have not been directly examined. Most studies include children aged 7–18 in a broad later onset of disease (LOD) group, making it difficult to determine the developmental course of cognitive changes in this age range. This is a serious omission, as later childhood is also a period of significant cognitive development. For example, qualitative changes occur in problem-solving and working memory in this age range, the consolidation of these skills coinciding with a peak in prefrontal and parietal gray matter at age 11–12 [55•, 56]. Consistent with this, Lin et al. [45••] found T1D/non-T1D group differences in working memory that were greater in participants with diabetes onset after age 5, and associated with chronic hyperglycemia, consistent with increased radial diffusivity reported in DTI studies [26]. Radial diffusivity is a predictor of working memory development in adolescence [57], probably because it provides an index of myelination, which in turn is related to efficient mental operations. Thus, there is converging evidence of a later effect of diabetes on the development of working memory, but the current data do not allow determination of whether this occurs in late childhood or adolescence.

Adolescence

From a psychosocial and behavioral standpoint, adolescence is arguably the period of greatest vulnerability for youth with T1D. Puberty brings physiological changes and increased stress that complicate diabetes management, and diabetes burnout and mental health issues such as depression are more likely to emerge at this time [58]. Adolescents also begin developing greater independence and autonomy, which can result in increased conflict with parents [59]. Many teens have the ability to understand diabetes and its management, but most lack the social-emotional maturity to maintain consistent adherence to the diabetes regimen. Together, these changes can result in a premature shift of diabetes responsibility from the parent to the adolescent [60•], just at a time when teenagers are more susceptible to risky decision-making [61]. All of these factors contribute to the poorer adherence and glycemic control that characterizes this period. Adolescents have A1c values up to 1 % higher than adults [62], and teenage girls have significantly higher incidence of DKA [63], placing them at heightened risk for hyperglycemia-mediated cognitive impairment.

Brain development also goes through marked changes in adolescence almost as dramatic as the changes in early childhood and old age [64]. Gray matter is reduced while white matter

increases as fibers become more myelinated. Subcortical structures such as the limbic system and striatum also go through dramatic changes that likely underlie increased reward-seeking behavior in the teenage years. Processing networks develop (and become more efficient) as a result of increased myelination, synaptic pruning, and synchronous firing (“integration through synchronization” [65]). Connections between the frontal lobes and other regions mature, with concurrent development of executive functions such as planning, organization, working memory, and impulse control. The so-called default mode network also matures at this time [66•]. While its exact functions remain under debate, the default network involves a distributed system including frontal lobes, posterior cingulate, and lateral parietal/occipital cortices (i.e., cuneus/precuneus) and is believed to be involved in introspective thinking of some sort [67].

This rapid development, coupled with increased glycemic dysregulation, may make adolescence an additional “crucial period” of CNS vulnerability to the impact of diabetes (especially hyperglycemia), with frontal networks and executive functions being more likely to show impairment [4]. This hypothesis is consistent with the “two-stage model” of behavioral development [68], which proposes that the perinatal period and adolescence represent distinct phases of hormonally driven nervous system (re)organization, and suggests that adolescence may be a second sensitive period of neurodevelopmental vulnerability.

Stress also has specific effects in adolescence, for example on prefrontal cortex [69], working memory [70], and emotional regulation [41], and there is emerging evidence that the effect of stress on prefrontal systems may be mediated by damage to white-matter microstructure [71]. Thus, increased stress may potentiate the deleterious effects of hyperglycemia on the CNS. Consistent with this, studies of adults with T1D onset in later childhood/adolescence have shown changes in white-matter integrity associated with reduced cognitive functioning [72].

The default network has become of interest in diabetes, as it has a very high resting glucose metabolism that makes it especially vulnerable to the impact of dysglycemia. Recent neuroimaging studies have consistently found gray- and white-matter changes in cuneus, precuneus [73, 74], and anterior cingulate [73]. Severe hypoglycemia and chronic hyperglycemia may both be associated with abnormal white matter in regions associated with this network [26, 75•], with the cuneus/precuneus being especially vulnerable to glycemic extremes [76]. The functional implications of these findings remain unclear, although it is interesting to speculate that insult in this region might affect individuals’ ability to think through possible outcomes related to completing or not completing diabetes management tasks. It has also been noted that this area is affected in early Alzheimer’s disease [77], making it a region of interest as a possible site of hyperglycemia-mediated accelerated cognitive aging [7].

Few studies have examined change in cognitive functioning in adolescents with T1D. In an older study by Fox et al. [78], adolescent boys did not make age-expected gains in verbal learning from 11–15 years, possibly because of the working memory demands of the task. A longitudinal analysis of 249 T1D patients in the DCCT who were 13–19 years old at the time of enrollment showed no decrement in cognitive performance an average of 18 years later

(range 15 to 23 years) [79]. Higher A1c was associated with decline in psychomotor speed and mental efficiency in these patients, but this effect was also found in the full cohort over the same period [80]. However, data are lacking on participants' glycemic history prior to enrollment, so the timing of these declines is unclear. In another longitudinal study, Northam et al. [46] found that older age at onset (exact ages not reported) predicted volume loss and T2 change in basal ganglia and thalamus, possibly reflecting "an interaction between type 1 diabetes and the final stages of neurodevelopment, with the early onset subgroup yet to experience this disruption."

So far, there is little evidence to support the hypothesis that T1D directly affects executive functioning in adolescence. McNally et al. [81] found that A1c did not predict parent-reported executive functioning. However, most of the children in this study (age range 9–11) had likely not reached puberty. In a longitudinal follow-up, Miller et al. [82] found no decline in executive functioning in these children, who were now 11–13 years old. Again, though, the relatively young age of the participants does not provide a strong test of the effects of diabetes across adolescence. Another study [83] did find impaired executive functioning in adolescents with T1D, although the effect was not associated with glycemic control.

In summary, there is currently limited evidence for specific cognitive effects of diabetes in adolescence compared to the strong evidence base of early-onset effects, despite the dramatic neurodevelopmental changes that occur during this period. Some studies suggest a selective vulnerability in working memory, but these findings are relatively limited. This may be due to limited research focused on older adolescents and a lack of studies directly examining more complex executive functions such as problem-solving or comparing cognitive outcomes in youth in good versus poor metabolic control. It is also likely due to the practice in most studies of placing all children older than seven in a broad "late onset" group. It is possible that childhood and adolescence contain multiple different sensitive periods tied to development of different brain areas and functions. Studies more closely parsing developmental effects of diabetes throughout the childhood and adolescent years are greatly needed.

Adulthood

Early adulthood and middle age represent a period of relative cognitive stability, whereas old age has been described as a renewed period of vulnerability [7]. However, there is evidence of subtle diabetes-related cognitive changes in adulthood. Jacobson et al. [80] noted declines in psychomotor speed and efficiency in an 18-year follow-up of the DCCT cohort. Asvold et al. [84] reported significant declines from childhood to adulthood in attention and problem-solving, although the exact timing of these declines is unclear.

Accelerated cognitive aging and increased risk for dementia have been documented in older adults with T2 diabetes [85], and it is plausible that T1D would also be associated with earlier cognitive decline. However, adolescents with T2 appear to have more significant deficits and earlier onset of neurological abnormalities than individuals with T1D [86•, 87], suggesting that the risk for accelerated aging is probably lower in T1D.

The few studies examining cognitive functioning in older adults with T1D seem to support this likelihood. Brands et al. [88] found slower information processing in patients 50 years and older with T1D, but the magnitude of change was comparable to the change in younger adults [80], and there were no differences on MRI compared to age-matched controls. A study of over 64,000 individuals 60 and older with T1D found elevated incidence of hypoglycemia and vascular complications, both of which could contribute to cognitive aging, but did not directly examine cognitive outcomes or integrity of the CNS [89]. Thus, the limited data available suggest that effects of T1D on aging are likely to be relatively subtle, although it is possible that diabetes-related dysfunction is more substantial in groups with greater neurocognitive risk.

Conclusions

In this paper, we provided a selective review of neurocognitive outcomes in pediatric diabetes (largely T1D) from a developmental perspective, integrating recent research from developmental neuroscience and neuroimaging. Many findings from the T1D literature resemble cognitive late-effects, with the strongest effect being the relationship between hyperglycemia, white-matter injury, and reduced information processing, with later-emerging decrements in IQ. Diathesis/ stress models provide a way to understand the complex patterns of neurocognitive outcomes in T1D, although relatively little research has examined potentially important diatheses such as genetic polymorphisms and environmental stress. Racial/ethnic differences in neurocognitive outcome have also received scant attention. Importantly, there may also be factors that protect against cognitive decline. For example, differences in *cognitive reserve*, which encompasses factors such as IQ and years of education, explain substantial variance in individual differences in susceptibility to dementia [90]. Investigations into possible risk and protective factors for cognitive change in diabetes should be a priority for future research.

An updated schematic of the neurodevelopmental model is presented in Fig. 1. Consistent with the model, cognitive effects of EOD are relatively global, encompassing gray-and white-matter changes throughout the brain, and affecting multiple areas of cognitive functioning. Severe hypoglycemia, hyperglycemia, and DKA all appear to play a role. At the same time, effects on the medial-temporal memory system appear largely confined to EOD, suggesting its heightened vulnerability in this age range. Cognitive effects in later childhood and adolescence are less clear, in part due to study designs and grouping strategies. We have suggested that adolescence might be an additional “crucial period” for cognitive vulnerability, given the dramatic neurodevelopmental changes that occur with onset of puberty and the concurrent behavioral risk that has long been known to influence diabetes management. Importantly, the risk of cognitive change in adolescence is not necessarily tied to *onset* at this age; children with earlier onset may also be at risk for emergence of “new” problems in adolescence in areas that undergo rapid maturation at this time, such as executive functioning. It is interesting to note that areas that appear to be affected later in development (basal ganglia, thalamus, default network, frontal lobes) all have high levels of inter-regional connectivity, which leads to the speculation that diabetes may primarily disrupt the formation and organization of functional networks at this stage, rather than affecting more discrete brain regions.

Clinically, it will be important to help parents understand the implication of cognitive vulnerability and late-effects, especially in children with early-onset diabetes who also experience glycemic extremes. Subtle cognitive decrements in areas such as processing speed and attention may only become evident over time, and parents can be counseled to watch for changes in school functioning so that difficulties might be caught early on. Parents and health care providers should also be aware of the possibility of newly emerging problems in executive functioning in adolescence and of the implications of executive dysfunction (e.g., problems with planning, organizing, and working memory) for illness self-management [91].

Many of the studies reviewed here did not find significant differences between individuals with T1D and matched controls; instead, significant findings appear to cluster around specific risk factors *within* the diabetes group, in particular EOD and poor glycemic control. Moreover, some studies suggest that effects of T1D may be driven by interactions between risk factors [45•]. These findings are in line with a diathesis/risk perspective that would suggest subgroups of children and youth with T1D may be at heightened risk for more severe cognitive dysfunction than has currently been reported in the literature. A greater understanding of the factors that contribute to or mitigate neurocognitive vulnerability in T1D could help guide eventual efforts to prevent cognitive complications. Identification of higher-risk subgroups is therefore a critical task facing future research.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect.* 2000; 108(Suppl 3):511–33. [PubMed: 10852851]
2. Stiles J, Jernigan TL. The basics of brain development. *Neuropsychol Rev.* 2010; 20:327–48. [PubMed: 21042938]
3. Pechtel P, Pizzagalli D. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology.* 2010; 214:1–3.
4. Desrocher M, Rovet J. Neurocognitive correlates of type 1 diabetes mellitus in childhood. *Child Neuropsychol.* 2004; 10:36–52. [PubMed: 14977514]
5. Ryan C. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. *Pediatr Diabetes.* 2006; 7:289–97. [PubMed: 17054452]
6. Ryan C. Searching for the origin of brain dysfunction in diabetic children: going back to the beginning. *Pediatr Diabetes.* 2008; 9:527–30. [PubMed: 19067890]
7. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol.* 2008; 7:184–90. [PubMed: 18207116]
8. Armstrong FD. Neurodevelopment and chronic illness: mechanisms of disease and treatment. *Ment Retard Dev Disabil Res Rev.* 2006; 12:168–73. [PubMed: 17061286]
9. Mulhern, RK.; Butler, RW. Neuropsychological late effects. In: Brown, R., editor. *Comprehensive handbook of childhood cancer and sickle cell disease: a biopsychosocial approach.* New York: Oxford University Press; 2006.
10. Turkel S, Pao M. Late consequences of chronic pediatric illness. *Psychiatr Clin N Am.* 2007; 30(4):819–35.

11. Beauchamp MH, Ditchfield M, Maller JJ, et al. Hippocampus, amygdala and global brain changes 10 years after childhood traumatic brain injury. *Int J Dev Neurosci.* 2011; 29:137–43. [PubMed: 21147212]
12. Taylor, HG. Children with very low birth weight or very preterm birth. In: Yeates, KO.; Ris, MD.; Taylor, HG., et al., editors. *Pediatric neuropsychology: research, theory, and practice.* 2. New York: Guilford; 2010.
13. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neuropsychological performance in school-aged children with surgically corrected congenital heart disease. *J Pediatr.* 2007; 151(1): 73–78. [PubMed: 17586194]
14. Vlassara H, Brownlee M, Cerami A. Excessive nonenzymatic glycosylation of peripheral and central nervous system myelin components in diabetic rats. *Diabetes.* 1983; 32:670–4. [PubMed: 6862112]
15. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care.* 2005; 28:726–35. [PubMed: 15735218]
16. Gaudieri PA, Chen R, Greer TF, Holmes CS. Cognitive function in children with type 1 diabetes: a meta-analysis. *Diabetes Care.* 2008; 31:1892–7. [PubMed: 18753668]
17. Naguib JM, Kulinskaya E, Lomax CL, Garralda ME. Neurocognitive performance in children with type 1 diabetes—a meta-analysis. *J Ped Psychol.* 2009; 34:271–82.
18. Northam EA, Anderson PJ, Werther GA, Warne GL, Adler RG, Andrewes D. Neuropsychological complications of IDDM in children 2 years after disease onset. *Diabetes Care.* 1998; 21:379–84. [PubMed: 9540019]
19. Northam E, Anderson P, Jacobs R, Hughes M, Warne G, Werther G. Neuropsychological profiles in children with type 1 diabetes 6 years after disease onset. *Diabetes Care.* 2001; 24:1541–6. [PubMed: 11522696]
20. Zuckerman, M. *Vulnerability to psychopathology: a biosocial model.* Washington, DC: American Psychological Association; 1999.
21. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth Study. *Pediatrics.* 2014; 133:e938–45.10.1542/peds.2013-2795 [PubMed: 24685959]
22. Glaser NS, Wootton-Gorges S, Buonocore M, Marcin JP, Rewers A, Strain J, et al. Frequency of subclinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes.* 2006; 7:75–80. [PubMed: 16629712]
23. Perantie DC, Lim A, Wu J, et al. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. *Pediatr Diabetes.* 2008; 9:87–95. [PubMed: 18208449]
24. Ghatti S, Lee JK, Sims C, DeMaster DM, Glaser NS. Diabetic ketoacidosis and memory dysfunction in children with type 1 diabetes. *J Pediatr.* 2010; 156:109–14. A small but well-designed study showing the effect of DKA on memory in children with early-onset disease. [PubMed: 19833353]
25. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res.* 2010; 107:1058–70. The most updated version of a highly influential model of the primary mechanisms for hyperglycemia-mediated cellular damage in diabetes and their role in diabetic complications. [PubMed: 21030723]
26. Antenor-Dorsey JA, Meyer E, Rutlin J, Perantie DC, White NH, et al. White-matter microstructural integrity in youth with type 1 diabetes. *Diabetes.* 2013; 62:581–9. [PubMed: 23139349]
27. Aye T, Reiss AL, Kesler S, et al. The feasibility of detecting neuropsychologic and neuroanatomic effects of type 1 diabetes in young children. *Diabetes Care.* 2011; 34:1458–62. [PubMed: 21562318]
28. Aye T, Barnea-Goraly N, Ambler C, et al. White-matter structural differences in young children with type 1 diabetes: a diffusion tensor imaging study. *Diabetes Care.* 2012; 35:2167–73. [PubMed: 22966090]
29. Marzelli MJ, Mazaika PK, Barnea-Goraly N, Hershey T, Tsalikian E, Tamborlane W, et al. Neuroanatomical correlates of dysglycemia in young children with type 1 diabetes. *Diabetes.* 2014; 63:343–53. The most recent neuroimaging findings from a large group of young children

with early-onset diabetes, demonstrating a relation between CNS changes and cognitive outcomes. [PubMed: 24170697]

- 30•. Barnea-Goraly N, Raman M, Mazaika P, Marzelli M, Hershey T, Weinzimer SA, et al. Alterations in white-matter structure in young children with type 1 diabetes. *Diabetes Care*. 2014; 37:332–40. The largest DTI study of a pediatric T1D cohort to date, demonstrating the effects of dysglycemia on white matter structure and integrity. [PubMed: 24319123]
31. Schwartz DD, Axelrad ME, Cline VD, Anderson BJ. Neurocognitive functioning in children and adolescents at the time of type 1 diabetes diagnosis: associations with glycemic control one year after diagnosis. *Diabetes Care*. 2014;10.2337/dc14-0103
32. Cato M, Mauras N, Ambrosino J, Bondurant A, Conrad AL, Kollman C, et al. Cognitive functioning in young children with type 1 diabetes. *J Int Neuropsychol Soc*. 2014; 20:238–47. [PubMed: 24512675]
33. Peila R, Rodriguez BL, Launer LJ. Type 2 Diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study. *Diabetes*. 2002; 51:1256–62. [PubMed: 11916953]
34. Ferguson SC, Deary IJ, Evans JC, Ellard S, Hattersley AT, Frier BM. Apolipoprotein-E influences aspects of intellectual ability in type 1 diabetes. *Diabetes*. 2003; 52:145–8. [PubMed: 12502505]
- 35•. Jacobson AM, Ryan CM, Cleary PA, et al. Diabetes Control and Complications Trial/EDIC Research Group. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. *Diabetologia*. 2011; 54:245–55. An 18-year follow-up of the DCCT cohort examining potential moderators of cognitive outcomes including biomedical and genetic factors. [PubMed: 20803190]
36. Hayes JD, Strange RC. Glutathione S-transferase polymorphisms and their biological consequences. *Pharmacology*. 2000; 61(3):154–66. [PubMed: 10971201]
37. Krull KR, Bhojwani D, Conklin HM, Pei D, Cheng C, Reddick WE, et al. Genetic mediators of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2013; 31:2182–8. [PubMed: 23650422]
38. Franco R, Schoneveld OJ, Pappa A, Panayiotidis MI. The central role of glutathione in the pathophysiology of human diseases. *Arch Physiol Biochem*. 2007; 113(4–5):234–58. [PubMed: 18158646]
39. Hovnik T, Dolžan V, Bratina NU, Podkrajšek KT, Battelino T. Genetic polymorphisms in genes encoding antioxidant enzymes are associated with diabetic retinopathy in type 1 diabetes. *Diabetes Care*. 2009; 32(12):2258–62. [PubMed: 19752172]
40. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. *Lancet*. 2012; 379:2291–9. [PubMed: 22683129]
41. Baker LM, Williams LM, Korgaonkar MS, Cohen RA, Heaps JM, Paul RH. Impact of early versus late childhood early stress on brain morphometrics. *Brain Imaging Behav*. 2013; 7:196–203. [PubMed: 23247614]
42. Ack M, Miller I, Weil WB. Intelligence of children with diabetes mellitus. *Pediatrics*. 1961; 28:764–70. [PubMed: 13859157]
43. Vannucci RC, Vannucci SJ. Glucose metabolism in the developing brain. *Semin Perinatol*. 2000; 24:107–15. [PubMed: 10805166]
44. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioral plasticity after early brain insult. *Brain*. 2011; 134:2197–221. [PubMed: 21784775]
- 45•. Lin A, Northam EA, Rankins D, Werther GA, Cameron FJ. Neuropsychological profiles of young people with type 1 diabetes 12 yr after disease onset. *Pediatr Diabetes*. 2010; 11:235–43. The most recent neurocognitive outcome data from a longitudinal study of a well-defined cohort of children with T1D followed since disease onset. [PubMed: 20070555]
46. Northam EA, Rankins D, Lin A, et al. Central nervous system function in youth with type 1 diabetes 12 years after disease onset. *Diabetes Care*. 2009; 32:445–50. [PubMed: 19151204]
47. Ho MS, Weller NJ, Ives FJ, Carne CL, Murray K, Vanden Driesen RI, et al. Prevalence of structural central nervous system abnormalities in early-onset type 1 diabetes mellitus. *J Pediatr*. 2008; 153:385–90. [PubMed: 18534238]

48. Languren G, Montiel T, Julio-Amilpas A, Massieu L. Neuronal damage and cognitive impairment associated with hypoglycemia: an integrated view. *Neurochem Int.* 2013; 63:331–43. [PubMed: 23876631]
- 49•. Blasetti A, Chiuri RM, Tocco AM, et al. The effect of recurrent severe hypoglycemia on cognitive performance in children with type 1 diabetes: a meta-analysis. *J Child Neurol.* 2011; 26:1383–91. The results of this meta-analysis suggest that recurrent severe hypoglycemia has a specific effect on learning and memory with milder effects on other areas of cognition. [PubMed: 21572053]
50. Bjørgaas MR. Cerebral effects of severe hypoglycaemia in young people with type 1 diabetes. *Pediatr Diabetes.* 2012; 13:100–7. [PubMed: 21790920]
51. Hershey T, Perantie DC, Wu J, Weaver PM, Black KJ, White NH. Hippocampal volumes in youth with type 1 diabetes. *Diabetes.* 2010; 59:236–41. [PubMed: 19833895]
52. Aggleton JP, Brown MW. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci.* 1999; 22:425–44. [PubMed: 11301518]
53. Palmer SL, Goloubeva O, Reddick WE, et al. Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. *J Clin Oncol.* 2001; 19:2302–8. [PubMed: 11304784]
54. Patiño-Fernández AM, Delamater AM, Applegate EB, et al. Neurocognitive functioning in preschool-age children with type 1 diabetes mellitus. *Pediatr Diabetes.* 2010; 11:424–30. [PubMed: 20456084]
- 55•. Crone EA, Ridderinkhof RK. The developing brain: from theory to neuroimaging and back. *Dev Cogn Neurosci.* 2011; 1:101–9. A conceptual review of brain development that links neuroscience approaches to more traditional views of cognitive development. [PubMed: 22436435]
56. Conklin H, Luciana M, Hooper C, Yarger R. Working memory performance in typically developing children and adolescents: behavioral evidence of protracted frontal lobe development. *Dev Neuropsychol.* 2007; 31:103–28. [PubMed: 17305440]
57. Ostby Y, Tamnes CK, Fjell AM, Walhovd KB. Morphometry and connectivity of the frontoparietal verbal working memory network in development. *Neuropsychologia.* 2011; 49:3854–62. [PubMed: 22001853]
58. Hood KK, Huestis S, Maher A, Butler D, Volkening L, Laffel LM. Depressive symptoms in children and adolescents with type 1 diabetes: association with diabetes-specific characteristics. *Diabetes Care.* 2006; 29:1389–91. [PubMed: 16732028]
59. Anderson BJ. Family conflict and diabetes management in youth: clinical lessons from child development and diabetes research. *Diabetes Spec.* 2004; 17:22–6.
- 60•. Anderson, BJ.; Schwartz, DD. Psychosocial and family issues in children with type 1 diabetes. In: Umpierrez, G., editor. *Therapy for diabetes mellitus and related disorders.* 6. American Diabetes Association; 2014. This book chapter reviews psychosocial issues faced by children and youth with diabetes and their families from a developmental perspective
61. Steinberg L. Risk-taking in adolescence: new perspectives from brain and behavioral science. *Curr Dir Psychol Sci.* 2007; 16:55–9.
62. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993; 329:977–86. [PubMed: 8366922]
63. Rewers A, et al. Predictors of acute complications in children with type 1 diabetes. *JAMA.* 2002; 287:2511–8. [PubMed: 12020331]
64. Colver A, Longwell S. New understanding of adolescent brain development: relevance to transitional healthcare for young people with long term conditions. *Arch Dis Child.* 2013; 98:902–7. [PubMed: 23986559]
65. Fair DA, Cohen AL, Dosenbach NUF, Church JA, Miezin FM, Barch DM, et al. The maturing architecture of the brain's default network. *Proc Natl Acad Sci U S A.* 2008; 105:1028–32.
- 66•. Blakemore SJ. Imaging brain development: the adolescent brain. *Neuroimage.* 2012; 61:397–406. A brief up-to-date review of recent neuroimaging findings of relevance to adolescent brain development. [PubMed: 22178817]

67. Buckner R, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann NY Acad Sci.* 2008; 1124:1–38. [PubMed: 18400922]
68. Sisk C, Zehr J. Pubertal hormones organize the adolescent brain and behavior. *Front Neuroendocrinol.* 2005; 26:163–74. [PubMed: 16309736]
69. Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. *Trends Neurosci.* 2008; 31:183–91. [PubMed: 18329735]
70. Hanson JL, Chung MK, Avants BB, Rudolph KD, Shirtcliff EA, Gee JC, et al. Structural variations in prefrontal cortex mediate the relationship between early childhood stress and spatial working memory. *J Neurosci.* 2012; 32:7917–25. [PubMed: 22674267]
71. Hanson JL, Adluru N, Chung MK, Alexander AL, Davidson RJ, Pollak SD. Early neglect is associated with alterations in white-matter integrity and cognitive function. *Child Dev.* 2013;10.1111/cdev.12069
72. van Duinkerken E, Schoonheim MM, Ijzerman RG, et al. Diffusion tensor imaging in type 1 diabetes: decreased white-matter integrity relates to cognitive functions. *Diabetologia.* 2012; 55:1218–20. [PubMed: 22327286]
73. Kaufmann L, Pixner S, Starke M, et al. Neurocognition and brain structure in pediatric patients with type 1 diabetes. *J Pediatr Neuroradiol.* 2011 Neurocognition and brain structure in pediatric patients with type 1 diabetes;
74. Perantie DC, Wu J, Koller JM, et al. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. *Diabetes Care.* 2007; 30:2331–7. [PubMed: 17575089]
75. Perantie DC, Koller JM, Weaver PM, et al. Prospectively determined impact of type 1 diabetes on brain volume during development. *Diabetes.* 2011; 60:3006–14. The results of this 2-year prospective neuroimaging study revealed within-diabetes group differences in whole brain gray matter associated with hyperglycemia and decreased occipital/parietal white matter associated with hypoglycemia. No differences were found between children with and without T1D. [PubMed: 21953611]
76. Arbelaez AM, Semenkovich K, Hershey T. Glycemic extremes in youth with T1DM: the structural and functional integrity of the developing brain. *Pediatr Diabetes.* 2013; 14:541–53. [PubMed: 24119040]
77. Buckner RL, Snyder AZ, Shannon BJ, et al. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci.* 2005; 25:7709–17. [PubMed: 16120771]
78. Fox MA, Chen RS, Holmes CS. Gender differences in memory and learning in children with insulin-dependent diabetes mellitus (IDDM) over a 4-year follow-up interval. *J Pediatr Psychol.* 2003; 28:569–78. [PubMed: 14602847]
79. Musen G, Jacobson AM, Ryan CM, Clearly PA, Waberski BH, Weinger K, et al. Impact of diabetes and its treatment on cognitive function among adolescents who participated in the Diabetes Control and Complications Trial. *Diabetes Care.* 2008; 31:1933–8. [PubMed: 18606979]
80. Jacobson AM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med.* 2007; 356:1842–52. [PubMed: 17476010]
81. McNally K, Rohan J, Pendley JS, Delamater A, Drotar D. Executive functioning, treatment adherence, and glycemic control in children with type 1 diabetes. *Diabetes Care.* 2010; 33(6): 1159–62. [PubMed: 20215458]
82. Miller MM, Rohan JM, Delamater A, Shroff-Pendley J, Dolan LM, et al. Changes in executive functioning and self-management in adolescents with type 1 diabetes: a growth curve analysis. *J Pediatr Psychol.* 2013; 38:18–29. [PubMed: 23027720]
83. Ohmann S, Popow C, Rami B, et al. Cognitive functions and glycaemic control in children and adolescents with type 1 diabetes. *J Psych Med.* 2010; 40(1):95–103.
84. Asvold BO, Sand T, Hestad K, Bjorgaas MR. Cognitive function in type 1 diabetic adults with early exposure to severe hypoglycemia: a 16-year follow-up study. *Diabetes Care.* 2010; 33:1945–7. [PubMed: 20805272]
85. Wrihten SA, Piroli GG, et al. A look inside the diabetic brain: contributors to diabetes-induced brain aging. *Biochim Biophys Acta.* 2009; 1792(5):444–53. [PubMed: 19022375]

- 86••. Bruehl H, Sweat V, Tirsi A, Shah B, Convit A. Obese adolescents with type 2 diabetes mellitus have hippocampal and frontal lobe volume reductions. *Neurosci Med.* 2011; 2:34–42. Along with the companion paper by Yau et al. below, the only examination of the effects of T2D on adolescent brain development. [PubMed: 21691448]
87. Yau PL, Javier DC, Ryan CM, et al. Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. *Diabetologia.* 2010; 53:2298–306. [PubMed: 20668831]
88. Brands AMA, Kessels RPC, Hoogma RP, et al. Cognitive performance, psychological well-being, and brain magnetic resonance imaging in older patients with type 1 diabetes. *Diabetes.* 2006; 55:1800–6. [PubMed: 16731845]
89. Schütt M, Fach EM, Seufert J, et al. For the DPV Initiative and the German BMBF Competence Network Diabetes Mellitus. Multiple complications and frequent severe hypoglycaemia in ‘elderly’ and ‘old’ patients with type 1 diabetes. *Diabet Med.* 2012; 29:e176–9. [PubMed: 22506989]
90. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med.* 2005; 25:1–14.
91. Duke DC, Harris MA. Executive function, adherence, and glycemic control in adolescents with type 1 diabetes: a literature review. *Curr Diab Rep.* 2014

Fig. 1.

An updated neurodevelopmental model. *Hypo*, hypoglycemia; *Hyper*, hyperglycemia; and *DKA*, diabetic ketoacidosis. The potential cognitive impact of diabetes is presumed to extend from time of onset forward, encompassing later developmental periods, so later-developing areas such as the default network would be considered vulnerable regardless of age of onset. *Solid lines* indicate areas in which changes have been documented in that age range; *dotted lines* represent time periods into which vulnerability may extend. *Dagger*, default network structures include cingulate cortex, cuneus, and precuneus