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Neurocognitive Deficits in Children with Chronic Health Conditions

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Abstract

Over 4 million children in the U.S. suffer from chronic health conditions including cancer, sickle cell disease and diabetes. Because of major advances in the early identification and treatment of these conditions, survival rates for these children continue to rise, and the majority now lives into adulthood. However, increases in survival have come with costs due to long-term effects of disease processes and treatments. Foremost among these consequences is impairment in brain development and neurocognitive function that may affect a substantial portion of children with chronic health conditions and follow many into adulthood. Impaired cognitive function may contribute to disruption in educational and occupational attainment, mental health, and quality of life for children with chronic conditions. In spite of the significance and scope of this problem, advances in the identification and understanding of neurocognitive problems and the delivery of effective clinical care have been hindered in part because research has been “siloed”---conducted on each chronic condition in isolation. This review examines for the first time neurocognitive problems in a selected set of six chronic pediatric health conditions--leukemia, brain tumors, sickle cell disease, congenital heart disease, type 1 diabetes, and traumatic brain injury--to define the magnitude of the problem and identify directions for future research and clinical care. Psychologists from many areas of specialization including pediatric psychology, educational and school psychology, neuropsychology, behavioral medicine, and adult primary care are uniquely positioned to contribute to every phase of this work including research, identification, and intervention.

Keywords

children; adolescents; chronic health conditions; neurocognitive problems

The health of America’s children is a picture in contrasts. On the one hand, over 80% of children in America are in excellent or very good health, and several major indicators of threats to child health, including rates of preterm births and infant mortality, have held steady or improved in recent years (National Institute of Child Health and Human Development, 2014). On the other hand, several factors have led to a significant increase in

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the number of children suffering from chronic health conditions (van der Lee, Mokkink, Grootenhuis, Heymans, & Offringa, 2007). Major advances in the early identification and treatment of a wide range of childhood health conditions have led to notable improvements in survival rates from formerly deadly diseases (Halfon & Newacheck, 2010). As a consequence, many diseases and health conditions that previously were often fatal in early childhood, including pediatric brain tumors, leukemia, sickle cell disease, and congenital heart disease (CHD), have become chronic childhood health conditions that continue through adolescence and into adulthood.

Many of the challenges associated with the increasing number of children with chronic health conditions are self-evident. These conditions place a growing burden on our health care system with heightened demands for acute, primary and tertiary care. Chronic health conditions are associated with decreased quality of life for many children and increased caretaking demands on parents (Cousino & Hazen, 2013). For example, the increase in survival rates among children with cancer has been described as a “double-edged sword” (Rosoff, 2006). The benefits of reduced mortality among children with cancer and other diseases/health conditions are immeasurable; however, these gains are countered by costs in long-term impairments in health and development. This double-edged sword is reflected in many other chronic health conditions as well, including CHD (Boulet, Grosse, Riehle-Colarusso, & Correa-Villasenor, 2010) and diabetes (Centers for Disease Control and Prevention [CDC], 2014).

One significant cost of chronic pediatric health conditions may be underestimated while increasing in prevalence and magnitude---many of these children experience problems in brain and cognitive development that last well into adulthood as a consequence of their condition and the treatments that are essential to their survival. Neurocognitive deficits may play a role in long-term impairment in educational and occupational attainment (Pang et al., 2008; Simko, McGinnis, & Schembri, 2006), as well as lower quality of life for children and their families (e.g., Hood et al., 2014; Lane, Lip, & Millane, 2002). Moreover, because neurocognitive problems associated with many chronic health conditions have been studied and treated in isolation from one another, the magnitude of the problem has gone relatively unrecognized, and opportunities for advances in research and clinical care may be missed.

In this review, we highlight findings from research on neurocognitive problems in children and adolescents with several selected chronic health conditions and identify unique and essential roles for multiple areas within psychology to address this large and growing public health problem. We begin by briefly summarizing prevalence rates of selected chronic health conditions for which meta-analyses of multiple studies of neurocognitive problems have been published. Second, we examine the evidence for neurocognitive impairments associated with these health conditions. Third, we review the effects of neurocognitive deficits on the lives of children and adolescents span childhood, adolescence, and into adulthood. Fourth, we highlight the diverse mechanisms by which chronic conditions affect brain development and cognitive functioning. Finally, we outline important directions for future research, practice, and advocacy. The evidence is compelling that psychologists from many areas of our field are needed at every stage of this phenomenon, including research, identification, and treatment.

Chronic Health Conditions in Childhood and Adolescence

For the purpose of this review, we conceptualize chronic health conditions as health or medical problems that last 3 months or more, require ongoing medical care, affect a child's normal activities, and are associated with functional impairment (van der Lee et al., 2007). The term "condition," is preferred over the terms "illness" or "disease," which often imply physical symptoms such fatigue, fever, or pain. As noted above, the epidemiology of many childhood health conditions in the United States has experienced a shift from acute to chronic illnesses, with the prevalence of chronic conditions in children rising in recent decades (e.g., van der Lee et al., 2007). Several factors have contributed to the increased prevalence in chronic health conditions including the early identification through the use of advanced technology and screening tools to more readily able to identify chronic conditions. Further, improved treatment through basic, translational, and clinical science has increased the survival rates of children with congenital disorders and serious health conditions. Moreover, the incidence and prevalence of several chronic health conditions have increased independent of early identification and successful treatments, particularly rates of some types of CHD and diabetes (CDC, 2014, 2015). At the broadest level, it is estimated that as many as 1 in 3 of America's 74 million children and adolescents, ages birth to 18 years, are living with a chronic health condition (e.g., Perrin, Bloom, & Gortmaker, 2007; van der Lee et al., 2007).

A salient example of the potential long-term effects of chronic health conditions can be found in childhood cancer. The Childhood Cancer Survivor Study (CCSS) is a large multi-institutional study following childhood cancer survivors into adulthood to better understand the long-term effects of cancer diagnosis and treatment (Robison et al., 2009). The original sample in the CCSS included a cohort of over 14,000 5-year survivors of pediatric and adolescent cancer who were diagnosed between 1970 and 1986 including survivors of a wide range of cancers (e.g., leukemia, brain tumors, Hodgkin's disease, non-Hodgkin's lymphoma, bone tumors). Survivors in this sample are at increased risk for a broad spectrum of adverse outcomes, including poor educational attainment, suboptimal employment status, and problems in interpersonal relationships, some of which may be related to cognitive deficits (Gurney, et al., 2009). The CCSS provides strong evidence that the effects of cancer and cancer treatments that are present in children persist into well into adulthood with associated impairments in a wide range of functioning including psychosocial functioning, health, and educational and work attainment (Cox et al., 2016; Pang et al., 2008). Similarly, research on adults with CHD indicates a significant difference in employment status as compared to healthy controls, despite similar levels of education (Simko et al., 2006).

The focus of this review is on a select subset of childhood health conditions for which there is a sufficient body of research examining possible neurocognitive impairments--leukemia, brain tumors, sickle cell disease, congenital heart disease (CHD), type 1 diabetes, and traumatic brain injury (TBI). For each of these conditions, research on neurocognitive problems has been examined in quantitative meta-analyses. We excluded other conditions (e.g., epilepsy, obesity, asthma, cystic fibrosis) which, although worthy of attention, lack sufficient data regarding neurocognitive functioning to determine the presence of adverse effects.

Prevalence of Selected Chronic Health Conditions in Childhood and Adolescence

Best estimates were compiled from the literature regarding the prevalence of the six selected chronic childhood health conditions associated with neurocognitive impairment. For each health condition a literature review was conducted, using PubMed, MedLine, Psycinfo, and the Centers for Disease Control and Prevention website. Data on age group, incidence rates, and survival rates were complied. After comparing data from various sources, we consulted with experts to determine accuracy of data. For some conditions, the data are clear on the number of children living with the condition; for conditions without readily identifiable prevalence data, we estimated the number of children living with a particular health condition by multiplying the incidence rate of the condition times the number of living children within a specific age group in the United States (i.e., 74.2 million children under the age of 18 years in the U.S.; U.S. Census Bureau, 2011), taking into account the survival rate, and age of onset of the condition.

Estimates of children with the six specific conditions include approximately 30,000 child/adolescent survivors of leukemia; 28,000 child/adolescent survivors of pediatric brain tumors; over 30,000 children and adolescents living with sickle cell disease;167,000 children and adolescents with type 1 diabetes; approximately 1,000,000 children and adolescents with CHD; and 3,045,000 children and adolescents with TBI. Thus, over 4 million children are living with one of these six chronic conditions. If even a fraction of these children experience neurocognitive problems, this potentially poses a significant burden on the healthcare and educational systems. These estimates may be the tip of the iceberg, both because many more children will be diagnosed in the years ahead and because these children transition to become adults living with chronic health conditions and their sequelae. We now turn to research on the magnitude of cognitive problems in children with specific chronic health conditions.

Neurocognitive Function in Children and Adolescents With Chronic Health Conditions: Exemplary Findings

The body of evidence on neurocognitive problems for chronic health conditions ranges widely. As noted above, for several chronic health conditions, the extent of neurocognitive problems is well-documented and reviewed in separate meta-analyses; we have chosen these conditions as the focus of the current review as more definitive conclusions can be drawn for these populations. For other important chronic health problems, research on neurocognitive problems is in its early stages and there are only a handful of published studies.

Meta-Analyses

We identified six childhood chronic health conditions for which at least one meta-analysis of neurocognitive effects has been published in a top-tier journal: leukemia, brain tumors, CHD, sickle cell disease, type 1 diabetes, and TBI (see Table 1). Effect sizes have been most often estimated using Cohen's *d* statistic, which is the standardized difference between two mean scores (i.e., the difference between the mean of the affected group and the healthy control or comparison group divided by the pooled standard deviation for the two groups). Meta-analyses also report Hedge's *g*; i.e., the difference in mean scores on measures of

cognitive function compared with healthy controls or norms weighted by the inverse of the variance. Using Cohen's rules of thumb, an effect size of .20 is a small effect, .50 is a medium effect, and .80 or greater is a large effect (Cohen, 1988). Cohen's *d* and Hedge's *g* can be transformed to reflect the difference in scaled score points. For example, an effect size of $d = 1.0$ corresponds to a difference of 15 points on a standardized measure of intelligence ($M = 100$, $SD = 15$).

Cancer: Leukemia—Impaired neurocognitive functioning is a well-documented long-term side effect of treatment for acute lymphocytic leukemia (ALL). A comprehensive meta-analysis of 28 studies conducted between 1980–2004 (Campbell et al., 2009) on long-term neurocognitive effects of childhood ALL, which included 1,005 cases and 1,141 healthy controls, revealed medium effect sizes for overall IQ ($g = -0.71$), verbal IQ ($g = -0.58$), and nonverbal IQ ($g = -0.66$). This corresponds to a mean difference of 10.65 points on full-scale IQ, placing the average ALL patient below 76% of their peers. Small to medium effect sizes were also found for measures of attention ($g = -0.57$), information processing ($g = -0.52$), executive functioning ($g = -0.46$), visuospatial skills ($g = -0.57$), verbal memory ($g = -0.39$) and visual memory ($g = -0.62$). Thus, ALL survivors consistently demonstrated significant deficits in intellectual functioning, as well as specific aspects of neurocognitive functioning. Medium effect sizes were also found for academic achievement ($g = -0.42$ to -0.60).

Cancer: Brain tumors—A meta-analytic review of 39 studies from 1992–2009 of the long-term neurocognitive effects in 1,318 survivors of pediatric brain tumors (Robinson et al., 2010a) revealed medium to large effect sizes ($g = -0.74$ to -0.88) for cognitive functioning, including full scale IQ ($g = -0.83$), verbal IQ ($g = -0.74$), and nonverbal IQ ($g = -0.88$). The large effect for full scale IQ translates to a mean difference of 12.45 IQ points between groups, placing the average brain tumor survivor below 80% of their peers. Large effect sizes were also noted for specific neurocognitive domains, including attention ($g = -1.22$), psychomotor skills ($g = -1.43$), visual-spatial skills ($g = -1.14$), and verbal memory ($g = -1.14$). Medium effect sizes were also found for academic achievement ($g = -0.45$ to -0.63). In general, neurocognitive effects for children with brain tumors are larger than those for children with ALL.

Congenital heart disease—A meta-analysis of 25 studies from 1980–2005 examined the impact of CHD on cognitive functioning in children and adolescents (Karsdorp, Everaerd, Kindt, & Mulder, 2007). A significant effect was found for overall cognitive ability (g = −0.25, CI = −0.47 to −0.02). Considerable heterogeneity existed among the findings, as disease severity was significantly related to overall cognitive functioning. In comparison with normative data, a large effect on full scale IQ ($g = -0.82$, n = 160) was found for children with hypoplastic left heart syndrome (HLHS), and a small effect ($g = -0.14$, n = 1108) was observed for children with transposition of the great arteries (TGA). Patients with HLHS had lower verbal ($g = -0.43$) and performance IQ ($g = -0.88$) than normative data, indicating that the average child with HLHS scored lower than 81% of their peers. Children with TGA had lower performance IQ scores ($g = -0.29$), corresponding to a score lower than 61% of their peers. In contrast, children with atrium septum defects (ASD)

and ventricular septum defects (VSD) showed cognitive functioning within the normative range. Thus, significant deficits in cognitive function are present for children with some type of CHD (HLHS, TGA) but not others (ASD, VSD).

Sickle cell disease—A meta-analysis of 18 studies conducted between 1963 and 2001, including 659 cases and 474 healthy controls, examined cognitive effects in children with sickle cell disease but without cerebrovascular injuries due to stroke (Schatz, Finke, Kellett, & Kramer, 2002). With regards to full scale IQ, a small effect was noted between children with SCD and comparison children ($g = -0.31$). This translated to a mean difference of 4.3 standard points between the two groups (i.e., the typical child with SCD scores lower than 62% of peers). Further, there were significant differences as a function of age, with a non-significant effect for full-scale IQ in children ages 9–10 years old (5 studies; $d = .06$), a significant small effect for children ages 10–11 years (5 studies; $d = -.33$), and a significant medium effect for children ages 11–13 years (5 studies; $d = -.57$). Consistent with these age differences, a recent study identified a decline of one IQ point for every increased year of age in a large sample of sickle cell patients (King et al., 2014). Schatz et al. (2002) also reported that 10 of 14 studies found differences in tests of specific cognitive abilities, with 8 out of 10 studies reporting significant differences in the domains of attention and executive functioning.

Type I diabetes—Twenty-four studies published between 1980 and 2005 were included in a meta-analysis of neurocognitive function in children with type 1 diabetes (Naguib, Kulinskaya, Lomax, & Garralda, 2009). Collectively, these studies sampled 894 cases of diabetes and 758 healthy controls. Small but statistically significant effects were reported for full-scale IQ ($d = -0.14$), performance IQ ($d = -0.18$), and verbal IQ ($d = -0.15$). This indicates that, compared to healthy controls, the average child with type 1 diabetes scored 2.1 points lower than their peers on measures of full-scale IQ. Diabetes was also associated with significantly poorer performance on measures of visuospatial ability ($d = -0.29$), motor speed ($d = -0.26$), and sustained attention ($d = -0.21$), as well as tests of and reading ($d = -0.23$) and writing ($d = -0.28$).

Traumatic Brain Injury—A meta-analysis of 28 studies conducted between 1988–2007 assessed neurocognitive outcomes in children who had experienced a TBI (Babikian & Asarnow, 2009). Severity of the injury was an important moderator of effects: small effects were found in children with mild brain injuries ($d = -.21$ for full scale IQ, $d = -.14$ for performance IQ, $d = -.22$ for verbal IQ, all non-significant). For moderate TBI, moderate to large significant effects were found for full scale IQ ($d = -.92$), verbal IQ ($d = -.67$), and performance IQ ($d = -.83$), decreasing over time. Finally, for severe TBI, large effects were noted for full scale IQ ($d = -.79$) and performance PIQ ($d = -.89$), which were sustained over time, and moderate effects were found for verbal IQ ($d = -.52$). Time since injury was also a moderator of the cognitive effects of TBI, such that longitudinal studies indicate greater recovery in some aspects of intellectual functioning (e.g., performance IQ) than others (e.g., verbal IQ).

Summary—This synthesis of research on neurocognitive deficits in children with chronic health conditions yields several notable findings. First, there is evidence of significant neurocognitive problems in children with a wide range of chronic health conditions, ranging from survivors of acute diseases, children with lifelong congenital problems, and those with problems that emerge during development. Large effect sizes were found for brain tumors, HLHS CHD, and moderate and severe TBI; medium effects were found for leukemia and sickle cell disease; and small effect sizes were found for type 1 diabetes, TGA CHD, and mild TBI. Second, the magnitude of neurocognitive problems is associated with other key factors such as age (e.g., SCD), severity (e.g., TBI), and time since diagnosis or disease onset (e.g., cancer). In spite of this variability, there is sufficient evidence for these problems in children to warrant concern. We therefore turn our attention to the implications of these effects and possible mechanisms underlying these effects that may inform potential targets for intervention.

Impact of Neurocognitive Impairment: What is at Stake?

As research continues to identify the magnitude and mechanisms of neurocognitive problems in children with chronic health conditions, it is important to consider possible short and long-term correlates of these effects in learning, achievement, employment, and well being.

Impact on Learning and Education

Given the strong correlation between full-scale IQ and subsequent academic achievement (i.e., as high as .80 over 5 years; Deary, 2012), the results summarized above indicating effects ranging from 2 to 13 or more lost IQ points as a result of a chronic health condition, suggest that these children may be at risk for subsequent declines in achievement. For example, a recent review on intelligence by Nisbett et al.(2012) underscores the importance of losses or gains of even 4 IQ points in relation to academic achievement. Moreover, the effects in children with the selected chronic health conditions reviewed in this paper are equal to or greater than the loss of IQ points associated with prenatal and perinatal lead exposure on childhood IQ, (Koller et al., 2004) and low birth weight (Ment et al., 2003), both major public health problems. Further, many aspects of neurocognitive functioning, such as attention, visual memory, verbal memory, information processing speed, and language are critical for success in school and work settings. These effects are reflected in the significant deficits in academic achievement documented in the meta-analyses for leukemia (Campbell et al., 2009), brain tumors (Robinson et al. 2010a, and diabetes (Karsdorp et al., 2007) cited above. It is important to note that the neurocognitive effects of chronic health conditions may be further compounded by the amount of time children spend out of school and in the hospital due to their medical condition can significantly impact their learning and academic success (Thies, 1999).

Impact on Earning Potential

The long-term effects of these cognitive deficits include possible diminished earning potential. For example, in the National Longitudinal Survey of Youth, for every 10-point decrease in IQ, there was an associated $2,000–6,000 loss in annual salary (Zagorsky, 2007).

Over an individual's lifetime, this amounts to a significant loss in potential income. Findings from the longitudinal CCSS with childhood leukemia survivors indicate an association between impairments in intellectual abilities and both unemployment and poorer educational attainment, and for CNS cancer survivors self-reported cognitive deficits were related to lower educational attainment, reduced income, and less full-time employment compared to controls (Kirchhoff et al., 2011; Kunin-Batson et al., 2011). Children with chronic health conditions are also more likely to receive income supplements for disability; 34% of youth receiving Social Security Disability Insurance were noted to have a chronic health condition (Perrin et al., 2007), and as noted above, adults with congenital heart disease and childhood cancer surivors are at increased risk for unemployment (Pang et al., 2008; Simko et al., 2006). While additional factors are likely to contribute to adverse effects on future work and employment (e.g., reduced vitality, health complications), neurocognitive problems are likely to influence these long-term outcomes.

Impact on Psychosocial Development and Mental Health

Impairments in executive functioning may compromise the ability to manage peer and family relationships, regulate emotions, and cope with stress, all of which contribute to increased risk for symptoms of anxiety, depression, and other mental health problems. For example, compared to siblings, long-term survivors of childhood brain cancer reported significantly more distress, particularly symptoms of depression, and had greater problems in interpersonal relationships (Zebrack et al., 2004). Similarly, children and adults with CHD and type 1 diabetes are at risk for symptoms of depression and poor quality of life (Hood et al., 2014), which may be related in part to neurocognitive dificits. For example, Robinson et al. (2015) found associations between impairment in activation in prefrontal brain regions in pediatric brain tumor survivors and social problems and the ability to cope with stress. These findings highlight the possible effects role of effects of cognitive problems on psychosocial functioning.

Mechanisms of Effect

The wide range of chronic health conditions associated with neurocognitive problems suggests that these effects may be the result multiple different mechanisms. Problems in cognitive function, and putative underlying aberrations in brain development, may represent processes of equifinality, or when a common phenotype--in this case cognitive impairment--is the result of multiple different etiologic pathways. We now consider the emerging evidence for possible causes of cognitive problems in children with chronic health conditions.

Disease-Related Mechanisms

Many of the pathophysiologic features of pediatric chronic health conditions likely have direct effects on brain development and subsequent neurocognitive functioning. Neural plasticity varies significantly with development (e.g., Kolb & Gibb, 2008), and disease-related processes may cause significant and lasting structural changes to the brain that damage and disrupt brain organization and development. These include tissue damage to the brain as a result of lesions (e.g., in brain tumors and stroke), impaired or disrupted delivery

of oxygen to the brain (e.g., hypoxia in sickle cell disease), chronic inflammation (e.g., circulatory levels of inflammatory cytokines), and impaired or disrupted delivery of glucose to the brain (e.g., diabetes).

Children who experience strokes and intraventricular hemorrhages suffer long-term neuropsychological impairment due to brain damage. Studies demonstrate a high prevalence of cerebral lesions in neonates with CHD, both pre and post-surgical intervention (von Rhein et al., 2011). Similarly, children with sickle cell disease are also at increased risk for strokes that lead to significant brain damage and impairment (Schatz et al., 2002). Research with children with sickle cell disease has shown that the magnitude of cognitive impairment is associated with the severity of brain damage; however, sickle cell disease patients with no MRI evidence of stroke still experience cognitive problems (King et al., 2014). These effects may be partially accounted for by other disease-related factors, such as cerebral oxygen deprivation and levels of inflammatory cytokines (e.g., Andreotti, Macy, King, Compas, & DeBaun, 2015).

Deficits may occur due to disrupted delivery of glucose to the brain in children with type 1 diabetes, who may suffer impairment in neurocognitive development due to frequent episodes of both hypoglycemia (low blood sugar) and hyperglycemia (high blood sugar) (Desrocher & Rovet, 2004). Maintaining glycemic control as close to normal as possible by administering insulin reduces the risk for micro- and macro-vascular complications, however, administering insulin to keep glucose levels closer to normal increases the risk for hypoglycemic episodes, which may negatively impact cognitive functioning (Desrocher & Rovet, 2004).

Treatment-Related Mechanisms

Many children are now surviving once-fatal illnesses because of aggressive and highly effective treatments, yet these treatments are often accompanied by significant neurocognitive late-effects. The most well documented examples come from the treatment of childhood cancer, as reflected in the adverse effects associated with radiation therapy and some forms of chemotherapy. For example, Kadan-Lottick et al. (2010) found deficits in executive function domains in leukemia and lymphoma survivors in the CCSS cohort who had undergone cranial radiation. Krull et al. (2013b) reported long-term deficits of 10 points in verbal IQ in adult survivors of childhood ALL treated with cranial radiation. Further, adult survivors of childhood Hodgkin lymphoma who were treated with thoracic (but not cranial) radiation also displayed deficits in cognitive function, suggesting an effect on brain function through cardiopulmonary dysfuction (Krull et al., 2012). More recent protocols for treatment of pediatric leukemia using chemotherapy are associated with a reduction in late effects compared with cranial radiation but there are still significant deficits in executive function skills (Cheung & Krull, 2015). Genetic differences in vulnerability to cognitive effects of chemotherapy and other medical treatments for cancer have also been identified (Kamdar et al., 2011; Krull et al. 2013a).

The use of functional neuroimaging methods has provided evidence of specific brain regions and processes that may be affected by cancer treatments. For some children treated for leukemia, chemotherapy is associated with reduced volume in the right prefrontal cortex, a

brain region responsible for higher order cognitive functions (Carey et al., 2008). Studies using functional magnetic resonance imaging (fMRI) suggest that disruption in function in the prefrontal cortex that may be the result of chemotherapy and radiation therapy in survivors of childhood leukemia (Robinson et al., 2010b) and brain tumors (Robinson et al., 2014; Robinson et al., 2015).

White Matter Development

Both disease and treatment-related factors may affect cognitive function through their impact on white matter development. Childhood and adolescence is a time during which white matter structures develop (Asato, Terwilliger, Woo, & Luna, 2010), and there is accumulating evidence that children with a wide range of chronic health conditions may experience reductions in white matter. For example, among survivors of pediatric brain tumors, white matter volume and integrity is related to impairments in memory, executive functions, executive functions, and IQ (e.g., Reddick et al., 2003; Riggs et al., 2014). These effects have been found in pediatric brain tumor survivors treated with chemotherapy without radiation (Liu et al., 2014). Similar associations were found in a study of survivors of childhood acute lymphoblastic leukemia, as smaller white matter volume was linked with deficits in attention, IQ, and academic achievement, with cranial irradiation linked to greater deficits (Reddick et al., 2006).

Similar patterns have been observed in children with CHD and diabetes. For example, significantly lower fractional anistotropy was observed in emerging adults with CHD as compared to controls (Brewster et al., 2015; Morton, Ishibashi, Jonas, & Gallo, 2015), and observed differences in structural white matter network topography in adolescents with CHD were associated with lower full scale IQ and deficits in executive function (Panigrahy et al., 2015). Children with type 1 diabetes exhibit significantly less growth of gray and white matter volume as compared to healthy controls, and changes in blood glucose levels were associated with changes in these volumes (Mazaika et al., 2016). For the conditions reviewed above, the most common domain of cognitive function in which impairments were evident was executive function skills, and Reddick et al. (2003) hypothesized that reduced white matter results in deficits in executive function, which then leads to lower IQ and academic achievement.

Poverty and Stress

Finally, *g*iven that chronic exposure to poverty has been associated with decreased neurocognitive functioning in young children, children with chronic health conditions who live in economically disadvantaged conditions may be at even greater risk for cognitive problems (Raver, Blair, & Willoughby, 2013). Childhood poverty has been linked with deficits in executive function through stress-related damage to the brain (Evans & Schamberg, 2009). Specifically, chronic childhood stress can lead to structural changes in the prefrontal cortex, as Hanson et al. (2012) found that greater adolescent stress was associated with smaller prefrontal cortex volumes and with poorer executive function. Therefore, children with chronic health conditions are exposed not only to illness-related stress, but they are often exposed to higher levels of multiple environmental stressors.

Summary

Although progress has been made in understanding possible mechanisms contributing to neurocognitive problems in children with chronic health conditions, research in this area has also been siloed. Increased understanding of these mechanisms can contribute to the development of targeted interventions improve cognitive function.

Future Directions: An Agenda for Research, Service Delivery and Public Policy

To date, clinical care and research have largely been conducted separately within each condition, limiting advances in understanding the scope of the problem, delaying advances in science, and potentially impeding the development and delivery of interventions to prevent or remediate these problems. Moreover, research on these chronic health conditions in children has been constrained by limits in research funding relative to similar problems in adults, as well as stigma attached to problems related to problems in brain development and mental health. Psychology is uniquely positioned to address these gaps.

Research on Effects and Mechanisms

Continued research is needed to document the pervasiveness of neurocognitive deficits and the mechanisms of these effects in children with chronic health conditions. Psychologists can lead the way in this cutting edge research. The growing body of evidence, summarized in meta-analyses reviewed above, demonstrates that neurocognitive deficits in children with chronic health conditions are a significant public health problem. However, several steps are needed in future research to examine these deficits with greater precision.

Emerging areas of research—Research on neurocognitive problems associated with many chronic health conditions is in its early stages and has not yet accumulated a sufficient body of evidence to warrant a meta-analysis. However, the prevalence and magnitude of effects found in early studies suggest that several of these conditions should be high priorities for future research. For example, there is evidence that a significant number of children who experience ischemic strokes experience impaired cognitive functioning and compromised executive functioning (e.g., Allman & Scott, 2013; Studer et al., 2014). Further, studies of children with epilepsy found that children with localization-related epilepsy with complex partial seizures showed mild deficits in general cognitive functioning, and that those with childhood absence epilepsy also showed deficits in verbal memory (Kernan et al., 2012; Pavone et al., 2001). These findings suggest that children with stroke and epilepsy are at increased risk for cognitive deficits, but more research is needed to determine the magnitude of these effects and their long-term consequences.

Greater precision in documenting magnitude and specificity of effects—Problems in cognitive function have been measured in a number of different domains including overall intelligence, verbal and nonverbal intelligence, aspects of executive function, and academic achievement. Synthesizing findings across domains of cognitive function is challenging, as deficits may vary widely across chronic conditions. Broad measures of cognitive function (e.g., full scale IQ) have been reported most often, with

additional data provided on more narrow domains of function when available. Psychologists bring unique training in the selection and interpretation of psychometrically sound measures of cognitive function.

Greater precision in documenting levels of cognitive deficits can also be achieved through careful selection of comparison groups. Studies have compared children with chronic conditions to both normative test samples and healthy children, including siblings and demographically matched peers, as benchmarks for determining the level of impairment. However, the comparison group that is selected may significantly affect the study outcome. For example, in a meta-analysis examining neurocognitive functioning in children with CHD, samples of healthy controls and siblings were both found to score significantly higher on cognitive functioning as compared to normative data (Karsdorp et al., 2007), suggesting that higher scores for selected control samples may affect the difference between affected children and controls. Therefore, it is important to account for the types of comparison samples used in estimating effect sizes for chronic health conditions.

Further, samples have included children with significant variation in the duration of their health condition, ranging from near the time of diagnosis, during treatment, and long-term survivorship. For conditions that are present at birth (e.g., CHD, sickle cell disease), children's age is synonymous with illness duration. For other conditions, however, such as leukemia and type 1 diabetes, time since diagnosis differs from age. Effects may vary as a function of time and aggregating effects without accounting for time/age is problematic.

Psychologists have been at the forefront of innovative research in behavioral medicine and neuroscience, and are therefore prepared to elevate this research to the next level. Building on large-scale studies such as those conducted by the Children's Oncology Group (COG) and the Silent Infarct Transfusion Trial for Sickle Cell Disease (e.g., King et al., 2014), further large-scale, multi-site studies are needed to understand the etiology, nature, and scope of neurocognitive deficits in children with chronic illness.

A more accurate understanding is needed of the number of children who are affected and the degree and specificity of their cognitive deficits. Specifically, research is needed to establish whether neurocognitive effects in children with chronic health conditions reflect actual declines in cognitive function or failure to make age-expected gains at the rate of healthy peers. Future research should continue to explore different mechanisms by which chronic health conditions contribute to neurocognitive deficits, and the specific domains that are affected, which would allow for targeted interventions. For example, recent imaging studies offer insight into which brain structures and regions are impacted (e.g., Robinson et al., 2014, 2015). Finally, greater understanding is needed of the effects of comorbid conditions, and whether multiple risk factors have additive or interactive effects to increase risk for cognitive deficits.

Research on Interventions

Psychologists can play an essential role in two important avenues for research on interventions to prevent or remediate neurocognitive problems in this population—testing

the effects of biomedical interventions on cognitive function and developing and testing novel psychological and behavioral interventions.

Documenting effects of biomedical treatments—There continues to be rapid development of new and novel biomedical treatments aimed at the management and, in some cases, cure of pediatric chronic health conditions. These new treatments are often by necessity aggressive and potentially toxic in their side effects including effects on cognitive function (see above). Alternatively, new treatments may lead to improved management of disease processes that could reduce the effects on brain development and function. Examples include the use of transfusions and hydroxyurea in the treatment of sickle cell disease to reduce the risk of stroke and increase the delivery of oxygenated hemoglobin to the brain (e.g., Sheehan et al., 2014). Psychologists need to partner with other members of pediatric care teams to monitor the effects of new and emerging treatments to identify both potential benefits and costs to children's cognitive function.

Develop and test innovative interventions—Preventive and remedial interventions are also needed to help children overcome cognitive problems and to improve their quality of life, and the specific domains impacted by chronic health conditions (e.g., working memory, attention) may be amenable to interventions. While some cognitive remediation programs, such as CogMed™ and Lumosity™, offer promise for improving function in areas such as working memory and sustained attention (e.g., Conklin et al., 2015; Hardy, Willard, Allen, & Bonner, 2013), more research is needed in larger randomized clinical trials to determine if the effects of these programs generalize to school and work settings (Olson & Sands, 2015). It is also unknown whether these programs will have the same effects in children with chronic health conditions as in the general population. Pharmacologic interventions may also play a role in treating specific cognitive problems. For example, methylphenidate, which has been traditionally prescribed for Attention Deficit/Hyperactivity Disorder, has been prescribed in cancer survivors to address problems with executive function (Conklin et al., 2010). Studies are needed in other conditions to determine when pharmacologic treatment is appropriate and psychologists are uniquely trained to measure outcomes in this population.

Further, many of these conditions occur at higher rates in youth living in poverty, who are already facing multiple challenges to academic success. The work of Evans and colleagues has identified the important role of parenting in children's cognitive development, most notably children growing up in poverty (e.g., Evans et al., 2007). Parenting may be another target, therefore, for preventive interventions. Promising evidence comes from a recent study showing that an intervention to enhance responsive parenting in low SES families led to improvements in cognitive and brain function in preschool age children (Neville et al., 2013).

Implications for Clinical Practice

The evidence summarized above has several implications for clinical practice based on the magnitude of the effects on cognitive development. Psychologists will play unique and essential roles in improving clinical practice for children with chronic health conditions. The

Psychosocial Standards of Care Project for Childhood Cancer (Weiner, Kazak, Noll, Patenaude, & Kupst, 2015) and scientific statement from the American Heart Association regarding evaluation and management of neurodevelopmental outcomes in children with CHD provide models for developing approaches to clinical practice (Marino et al., 2012). Specifically, regarding neurocognitive function in pediatric cancer patients and survivors, the group recommended, “Children with brain tumors and others at high risk for neuropsychological deficits as a result of cancer treatment should be monitored for neuropsychological deficits during and after treatment” (Annett, Patel, & Phipps, 2015, p. S460).

These standards of practice for pediatric oncology and CHD can be used to guide practice with other chronic illness populations. For children who have health conditions with large effects on cognitive function, including CHD (specifically HLHS) and moderate to severe TBI, testing may be warranted as early as possible in the course of the health condition. For conditions characterized by a clearly delineated diagnosis, such as leukemia, brain tumors, and TBI, conducting testing at the time of diagnosis will provide a baseline for evaluating future cognitive function (e.g., Thigpen et al., 2016). For other conditions that are present from birth, such as congenital heart defects, testing should begin as early in development as possible to allow for rapid identification of children at risk for delays and deficits in later cognitive development. Monitoring of cognitive function should continue through testing at regular intervals during a child’s care, including important treatment-related events (initiation of treatment, changes in dosage, completion of treatment). Clinical child psychologists, pediatric neuropsychologists, and school psychologists have the requisite training and expertise to serve in this role in these settings. Further, testing could continue into adulthood to monitor the long-term effects of these childhood conditions, requiring a transition to psychologists with training in adult neuropsychology. Significant barriers to services remain including the availability of pediatric neuropsychology specialists, the costs of comprehensive neuropsychological assessment, and inconsistent reimbursement for such services by third party payers (Annett et al., 2015)

For children with conditions for which there is evidence of mild cognitive deficits, such as type 1 diabetes and sickle cell, we suggest educating families as to the risks for these deficits, and using brief screening tools to identify those at greatest risk. Therefore, physicians, nurses, psychologists, and educators also need education and training to recognize, diagnosis, and treat these important problems. In addition, we recommend that multi-site consortiums of specific conditions (e.g., COG; Type 1 Diabetes Exchange Clinical Network) include neurocognitive testing as part of their cooperative studies. With these large sample sizes, we will learn more about the most affected domains, and we can make more precise recommendations. For conditions with small effects on neurocognitive functioning, accommodations, such as preferential seating or extended time for test taking, may be sufficient.

Advocacy and Public Policy

A final role for psychologists is to lead advocacy efforts to increase access to care for children with chronic health conditions. For example, inadequate health insurance is a key

barrier to access to monitoring and care for late effects, including neurocognitive problems, in cancer survivors (Annett et al., 2015). Some children with chronic health conditions suffer significant deficits in these functions that may go undiagnosed, misunderstood, and untreated within our educational system (e.g., Kudera & Sullivan, 2011). There is a need to move toward a more integrated model of health care and prevention, and psychologists are needed at every stage of development. The Patient Protection and Affordable Care Act (2010) builds on the Mental Health Parity and Addiction Equity Act of 2008 to provide parity and expand coverage for mental health conditions (Fisher & Dickinson, 2014), which may provide opportunities for this emerging area. Psychologists can lead efforts to increase screening, monitoring and access to care for children with chronic health conditions whose cognitive function has been impaired.

Conclusion

The chronic health conditions reviewed are associated with significant neurocognitive problems, ranging from small to large effects. While research examining the mechanisms, correlates, and consequences of cognitive deficits has made progress, there has been little crosstalk between conditions. In this paper, we highlighted the overlap in cognitive deficits across chronic health conditions, including overall intelligence, verbal and non-verbal intelligence, and aspects of executive functions. Given that millions of children in the United States are living with chronic health conditions, the number of children at risk for cognitive problems is a true hidden epidemic. It is time for psychology to spearhead the effort to better understand the score and nature of these problems and deliver much needed evidence-based services to this population.

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Biographies

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Table 1

Results of intellectual functioning from meta-analyses of children with selected chronic health conditions.

Health Condition	Number of Studies	Domains	Comparison Group	Effect Size (*d* or *g*)	Effect Size (IQ points)
Type 1 diabetes (Naguib et al., 2009)	24	PIQ	Healthy control	d = −0.18	−2.7
		VIQ	Healthy control	d = −0.15	−2.25
		FSIQ	Healthy control	d = −0.14	−2.1
Congenital heart defects (HLHS) (Karsdorp et al., 2007)	4	PIQ	Normative sample	g = −0.88	−13.2
		VIQ	Normative sample	g = −0.43	−6.45
		FSIQ	Normative sample	g = −0.82	−12.3
Congenital heart disease (TGA) (Karsdorp et al., 2007)	11	PIQ	Normative sample	g = −0.29	−4.35
		VIQ	Normative sample	g = −0.05	−0.75
		FSIQ	Normative sample	g = −0.14	−2.1
Sickle cell disease (Schatz et al., 2002)	18	FSIQ	Healthy control	g = −0.31	−4.3
Leukemia (Campbell et al., 2009)	28	PIQ	Healthy control	g = −0.71	−10.65
		VIQ	Healthy control	g = −0.58	−8.7
		FSIQ	Healthy control	g = −0.66	−9.9
Brain tumors (Robinson et al., 2010)	39	PIQ	Normative sample	g = −0.88	−13.2
		VIQ	Normative sample	g = −0.74	−11.1
		FSIQ	Normative sample	g = −0.83	−12.45
Traumatic Brain Injuries (mild) (Babikian & Asarnow, 2009)	28	PIQ	Healthy control	g = −0.22	−3.3
		VIQ	Healthy control	g = −0.14	−2.1
		FSIQ	Healthy control	g = −0.21	−3.15
Traumatic Brain Injuries (moderate) (Babikian & Asarnow, 2009)	28	PIQ	Healthy control	g = −0.83	−12.45
		VIQ	Healthy control	g = −0.67	−10.05
		FSIQ	Healthy control	g= −0.92	−13.8
Traumatic Brain Injuries (severe) (Babikian & Asarnow, 2009)	28	PIQ	Healthy control	g = −0.89	−13.35
		VIQ	Healthy control	g = −0.52	−7.8

Health Condition	Number of Studies	Domains	Comparison Group	Effect Size (*d* or *g*)	Effect Size (IQ points)
		FSIQ	Healthy control	g = −0.79	−11.85