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INTRODUCTION

Down Syndrome: Cognitive and Behavioral Functioning Across the Lifespan

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Individuals with Down syndrome (DS) commonly possess unique neurocognitive and neurobehavioral profiles that emerge within specific developmental periods. These profiles are distinct relative to others with similar intellectual disability (ID) and reflect underlying neuroanatomic findings, providing support for a distinctive phenotypic profile. This review updates what is known about the cognitive and behavioral phenotypes associated with DS across the lifespan. In early childhood, mild deviations from neurotypically developing trajectories emerge. By school-age, delays become pronounced. Nonverbal skills remain on trajectory for mental age, whereas verbal deficits emerge and persist. Nonverbal learning and memory are strengths relative to verbal skills. Expressive language is delayed relative to comprehension. Aspects of language skills continue to develop throughout adolescence, although language skills remain compromised in adulthood. Deficits in attention/executive functions are present in childhood and become more pronounced with age. Characteristic features associated with DS (cheerful, social nature) are personality assets. Children are at a lower risk for psychopathology compared to other children with ID; families report lower levels of stress and a more positive outlook. In youth, externalizing behaviors may be problematic, whereas a shift toward internalizing behaviors emerges with maturity. Changes in emotional/behavioral functioning in adulthood are typically associated with neurodegeneration and individuals with DS are higher risk for dementia of the Alzheimer's type. Individuals with DS possess many unique strengths and weaknesses that should be appreciated as they develop across the lifespan. Awareness of this profile by professionals and caregivers can promote early detection and support cognitive and behavioral development.

KEY WORDS: Down syndrome; neurocognitive; neurobehavioral; development

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INTRODUCTION

John Langdon Down initially identified Down syndrome (DS) approximately 150 years ago [Down, 1866]. DS is the genetic manifestation of trisomy of chromosome 21 [Rahmani et al., 1989; Delabar et al., 1993; Korenberg et al., 1994; Constestabile et al., 2010]. DS is associated with neuropathological alterations in both neuronal proliferation and differentiation [Pulsifer, 1996], manifesting in alterations in cognitive and behavioral functioning across the lifespan. DS is estimated to occur once in every 700–800 live births with a global incidence of more than 200,000 cases per year [Constestabile et al., 2010]; however, this may be an underestimate of the incidence during pregnancy due to the rate of both spontaneous and elective abortions [Hsu, 1998; Ethan and Canfield, 2002; Skotko, 2009]. The diagnosis of DS is typically made through genetic karyotype testing, with post-natal confirmation via the identification of characteristic syndrome-based physical and/or medical features [Siegel and Smith, 2010]. The distal part of the

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long arm of chromosome HSA21 is recognized as the "Down syndrome critical region" and it is specifically associated with intellectual disability (ID) [Rahmani et al., 1989; Delabar et al., 1993; Korenberg et al., 1994; Constestabile et al., 2010]. Phenotypic manifestations of DS have been identified and are discussed here.

COGNITIVE FUNCTIONING

General Intelligence

ID is recognized as one of the most prominent features of DS [Vicari et al., 2005; Constestabile et al., 2010] and DS is the most common genetic etiology of ID [Pulsifer, 1996; Anderson et al., 2013; Daunhauer et al., 2014]. The severity of ID among individuals with DS falls on a spectrum that ranges from profound to borderline intellectual functioning (Intelligence Quotient [IQ] = 30–70; mean IQ = 50) [Vicari et al., 2005; Constestabile et al., 2010], with most individuals demonstrating moderate to severe ID [Nelson et al., 2005; Lott and Dierssen, 2010]. Cognitive functioning often changes across the lifespan and is moderated by several comorbid factors such as sensory impairments, seizures, autism, sleep disruption, and other medical and psychiatric conditions [Gasquoine, 2011].

Cognitive growth persists through childhood, adolescence and early adulthood [Carr, 2005; Couzens et al., 2012] and is followed by a gradual loss of abilities [Oliver et al., 1998; Carr, 2005] commonly associated with a dementia process [Devenny et al., 2000; Maatta et al., 2006]. While standardized test scores appear to drop [Dameron, 1963; Share et al., 1964; Carr, 1970, 1988, 2000, 2005; Dicks-Mireaux, 1972; Shonkoff et al., 1992; Crombie and Gunn, 1998; Miller, 1998; Hauser-Cram et al., 1999; Couzens et al., 2011], analysis of raw scores reveals the acquisition of skills at a slower rate of cognitive growth, rather than loss of skills [Carr, 1988; Crombie and Gunn, 1998; Couzens et al., 2011, 2012]. In middle to late adulthood, test interpretation shifts from an emphasis on cognitive development to assessment for cognitive decline. When declines are observed on testing, they often reflect a loss of previously acquired skills relative to one's own prior abilities [Nadel, 2003; Pennington et al., 2003; Constestabile et al., 2010].

Within the domains of cognitive functioning, individuals with DS demonstrate a consistent pattern of weaknesses in the processing of verbal information relative to visual information [Gibson, 1978; Pueschel et al., 1987; Pulsifer, 1996; Rondal and Edwards, 1997; Miller, 1999; Abbeduto et al., 2001]. Children with DS continue to make gains in nonverbal cognitive abilities [Couzens et al., 2011; Channell et al., 2014a], whereas the growth of verbal abilities tends to decelerate throughout adolescence and into adulthood [Carr, 2000, 2005; Kittler et al., 2004; Naess et al., 2011]; however, this does not indicate that individuals' raw scores become stagnant [Chapman et al., 2002].

Longitudinal studies through middle adulthood reveal continued declines in standardized test scores with increasing age [Dameron, 1963; Share et al., 1964; Carr, 1970, 1988, 2000, 2005; Dicks-Mireaux, 1972; Shonkoff et al., 1992; Crombie and Gunn, 1998; Miller, 1998; Hauser-Cram et al., 1999; Couzens et al., 2011]. Cognitive declines in middle to late adulthood are frequently associated with a dementia of the Alzheimer type, although neurodegenerative changes can take place even in the absence of clinical signs of dementia. Accelerated volume loss is observed across the frontal, temporal, and parietal lobes [Teipel et al., 2004; Haier et al., 2008; Beacher et al., 2010; Anderson et al., 2013] and reduced connectivity is demonstrated, reflecting impaired ability to integrate information from distant brain regions into coherent distributed networks [Lott and Dierssen, 2010; Anderson et al., 2013]. Specific cognitive domains will be discussed below.

Language

Early language milestones (e.g., babbling) are typically met within an age-expected range [Smith and Oller, 1981; Oller and Siebert, 1988; Steffens et al., 1992; Thoradottir et al., 2002]; however, infants show reduced vocal reactivity and responsiveness to the environment [Kasari et al., 1990; Jahromi et al., 2008]. Delayed acquisition of a child's first words is observed [Laws and Bishop, 2003; Levy and Eilam, 2013]. Early in life, single word vocabulary, the intentional use of communication, and the pragmatic aspects of language are commonly recognized as strengths [Owens and MacDonald, 1982; Coggins et al., 1983; Tannock, 1988; Beeghly et al., 1990; Roberts et al., 2007; Couzens et al., 2011]. As the language demands increase, a delay in the use of multi-word phrases and atypical patterns of communication is demonstrated [Oliver and Buckley, 1994; Sigman and Ruskin, 1999]. Consistent delays in language skills are observed once the child reaches age five [Guralnick, 2002; Rondal, 2006].

Language profiles of school-aged children reveal a significant delay in expressive language relative to receptive language development, with the greatest delays in expressive syntax and phonological processing [Chapman et al., 2002; Chapman, 2006]. More specifically, language syntax (including use of verbs, nouns, pronouns, grammatical morphemes, and sentence structure) is particularly challenging both in terms of verbal expression and comprehension [Beeghly et al., 1990; Hulme and Mackenzie, 1992; Fowler et al., 1994; Rondal, 1994; Kernan and Sabsay, 1996; Rondal and Edwards, 1997; Miller, 1999; Chapman and Hesketh, 2000 ; Eadie et al., 2002; Vicari et al., 2002; Abbeduto et al., 2003; Vicari, 2004; Abbeduto and Chapman, 2005; Miolo et al., 2005; Chapman, 2006; Estigarriba et al., 2012; Levy and Eilam, 2013]. Aspects of language therefore develop unevenly and the discrepancy continues to grow with age [Chapman et al., 1991; Rondal, 1994; Miller, 1995; Chapman, 2003; Joffe and Varlokosta, 2007; Constestible et al., 2010].

Relative strength in single word receptive vocabulary is also present during adolescence; however, the ability to comprehend more complex language

syntax may plateau in late childhood or early adolescence [Chapman et al., 2002, 2006]. Syntactic weakness is most prominent during late childhood/early teenage years [Miller, 1999], particularly when viewed in comparison with typically developing (TD) peers. In adulthood, language deficits in articulation, phonological processing, and morphosyntax remain diminished; however, semantic, pragmatic, and communicative intent are relatively preserved [Pulsifer, 1996; Rondal and Comblain, 1996; Estigarriba et al., 2012] and generally consistent with or slightly above mental age (MA) (mean intellectual performance for a specific age) [Pulsifer, 1996]. Overall, comprehension of language remains limited and individuals often attempt to rely on lexical and situational cues to make meaning of what is said to them [Rondal and Comblain, 1996]; however, even these aspects of language processing are weak relative to TD peers [Bello et al., 2014]. As individuals continue to mature, speech comprehension and production slow further, there are higher rates of dysfluencies (hesitation, pauses), word discrimination becomes more difficult, and speech organization/word retrieval problems emerge [Rondal and Comblain, 1996]. Some of these difficulties may be attributed in part to age-related changes in hearing, auditory discrimination, and less efficient respiratory support for speech [Rondal and Comblain, 1996].

Impaired processing in aspects of language comprehension can adversely impact other aspects of cognition such as learning and memory. Lexical access, syntactic awareness, and phonological skills are reduced in individuals with DS, particularly if articulation does not develop to an automatic level or if representations of phonemic sequences fail to be consolidated into long-term semantic memory [Gathercole and Baddeley, 1989; Gathercole et al., 1991; Adams and Gathercole, 1995, 2000; Grossberg and Myers, 2000; Laws, 2002; Laws and Gunn, 2004; Miolo et al., 2005; Conners et al., 2008]. Similarly, cognitive functioning in other domains also impacts language development. Weakness in verbal processing is believed to be secondary to deficits in the phonological loop, an aspect of verbal working memory, which likely contributes to problems with structural language and weaknesses in phonological processing, and in sentence imitation [Broadley et al., 1995; Pulsifer, 1996; Chapman and Hesketh, 2001; Jarrold and Baddeley, 2001; Laws, 2002; Hodapp and Dykens, 2004; Laws and Gunn, 2004; Brock and Jarrold, 2005; Fidler, 2005; Miolo et al., 2005; Purser and Jarrold, 2005; Chapman, 2006; Vicari and Carlesimo, 2006; Silverman, 2007; Couzens et al., 2011]. Language development is therefore dependent on and contributes to more global cognitive functions.

When comparing individuals with DS to other individuals with ID of differing etiologies, linguistic development is delayed beyond other groups [Abbeduto et al., 2008] and it qualitatively differs in nature [Polisenska and Kapalkova, 2014]. Relative to individuals with Williams and fragile X syndromes, individuals with DS have even greater delays in morphosyntactic skill development [Estigarriba et al., 2012; Levy and Eilam, 2013] and poor articulation and speech intelligibility [Hulme and Mackenzie, 1992; Fowler et al., 1994; Miller, 1999; Abbeduto and Chapman, 2005; Chapman, 2006]. In contrast, language pragmatics and conversational style appear consistent with MA [Beeghly et al., 1990; Rondal, 1994; Rondal and Edwards, 1997] and may be viewed as areas of strength relative to individuals with other genetic-related ID.

Attention/Executive Functions

Executive functions (EF), at the lower level involve the regulatory components of behavior and cognition including aspects of attention, inhibition, and processing speed [Alvarez and Emory, 2006]. Higher level EF include higher ordered cognitive processes of information processing that include strategic planning, impulse control, organized search, flexibility of thought and action [Alvarez and Emory, 2006]. Higher level EF also include the ability to integrate what a person wants to do with what they can do, self-monitor behavior, and direct energy toward achieving a future goal [Alvarez and Emory, 2006; Willoughby et al., 2014].

Older studies of EF in individuals with DS demonstrate deficits on tasks of attention, perceptual speed, reaction time, and motor control [Berkson, 1960; Meyers et al., 1961; Clausen, 1968; Nettlebeck and Brewer, 1976; Logan, 1985] relative to adolescents with matched MA [Meyers et al., 1961]. Weaknesses in simultaneous and successive processing and organization of motor responses are also observed when compared with peers with ID of other etiologies [Snart et al., 1982; Lincoln et al., 1985]. Recent studies demonstrate more varied results among individuals evaluated early in the lifespan, whereas studies in adulthood show evidence of deficits more consistently. For example, in childhood some studies show aspects of preserved EF skills relative to individuals matched for MA [Vicari et al., 2000; Pennington et al., 2003; Lanfranchi et al., 2010; Costanzo et al., 2013], whereas other studies demonstrate impairment in aspects of EF for individuals with DS, even relative to other individuals with ID [Trezise et al., 2008; Costanzo et al., 2013]. Discussion of salient findings by EF domain is outlined below.

Attention

Children with DS show impairment in many aspects of attention (e.g., auditory sustained attention, visual selective attention) that extend beyond that expected for MA [Rowe et al., 2006; Porter et al., 2007; Trezise et al., 2008; Kogan et al., 2009; Lanfranchi et al., 2010; Rhodes et al., 2010; Lee et al., 2011; Costanzo et al., 2013]. Selective attention deficits persist through adulthood [Cornish et al., 2001; Rowe et al., 2006; Breckenridge et al., 2013] and contribute to difficulty prioritizing, staying engaged with a task, and consistently responding in the same manner to certain situations, thus limiting one's ability to function and ultimately reside independently.

Inhibition

Poor response inhibition is evident across the developmental lifespan, emerging in toddlers and continuing through adulthood [Cornish et al., 2007; Edgin et al., 2010; Lanfranchi et al., 2010]. Greater difficulty is evident on verbally mediated inhibition tasks relative to visually mediated ones [Munir et al., 2000; Pennington et al., 2003; Borella et al., 2013; Costanzo et al., 2013]. Poor inhibition of irrelevant information is also demonstrated in toddlers, school-aged children, and adolescents [Cornish et al., 2007; Borella et al., 2013], suggesting a generalized deficit in inhibitory control.

Processing Speed

Evaluation of reaction times show mixed results, with speed of reaction time shown to be consistent with intellectual functioning [Silverman and Kim, 1997], but slower reaction time relative to individuals with MA matched individuals with ID [Brunamonti et al., 2011].

Short-Term/Working Memory

Studies across the lifespan have consistently demonstrated that auditory working memory is less developed than visuospatial working memory [McDade and Adler, 1980; Marcell and Weeks, 1988; Hulme and Mackenzie, 1992; Bower and Hayes, 1994; Marcell et al., 1995; Seung and Chapman, 2000; Jarrold et al., 2002; Lanfranchi et al., 2004, 2009; Hick et al., 2005; Miolo et al., 2005; Chapman, 2006; Abbeduto et al., 2008; Conners et al., 2008; Frenkel and Bourdin, 2009; Lott and Dierssen, 2010; Levy and Eilam, 2013]. Deficits in verbal working memory extend beyond that observed in other individuals with ID, as well as beyond that which is expected for individuals with hearing and speech articulation difficulties, with differences evident even in young, school-aged children that persist throughout adulthood [Marcell et al., 1988; Marcell and Weeks, 1988; Bower and Hayes, 1994; Jarrold and Baddeley, 1997; Jarrold et al., 2002; Conners et al., 2008].

In school-aged children and adolescents, further studies have suggested that reduced verbal working memory may reflect the absence of active rehearsal [Jarrold et al., 2000; Vicari, 2004; Silverman, 2007]; however, Broadly and colleagues [1995] propose that a subvocal rehearsal strategy for storing and recalling verbally presented items is employed. Interestingly, when examined longitudinally syntax comprehension is associated with working memory (auditory and visual) [Chapman et al., 2002], demonstrating the relationship between working memory (across both modalities) and its interrelatedness with continued language acquisition.

From childhood and persisting across the lifespan, visuo-spatial short-term memory remains relatively spared compared to verbal working memory, on tasks with brief amounts of information or when visual and spatial components are assessed separately [Jarrold and Baddeley, 1997; Jarrold et al., 2000, 2002; Numminen et al., 2001; Seung and Chapman, 2004; Lanfranchi et al., 2004; Vicari, 2004; Rowe et al., 2006; Visu-Petra et al., 2007]. As the amount of information that needs to be processed increases (e.g., combined visual and spatial components), performance is compromised in children and adolescents relative to MA matched controls [Lanfranchi et al., 2004; Visu-Petra et al., 2007], likely secondary to limitations in working memory storage capacity.

Planning/Organization

Children with DS show difficulty executing a strategy to problem-solve [Lanfranchi et al., 2010]. For many individuals with DS, poorly organized approaches to learning new skills and difficulty rehearsing new information contribute to slowed developmental progress [Gilmore and Cuskelly, 2009; Lott and Dierssen, 2010]. As children with DS mature, they take longer to execute actions in planning tasks, but are able to perform similarly with regard to accuracy to MA matched controls [Vicari et al., 2000; Pennington et al., 2003; Rowe et al., 2006].

Set-Shifting/Multitasking

Shifting mental set is particularly challenging for children and adults with DS [Rowe et al., 2006; Costanzo et al., 2013], especially on verbally-mediated tasks [Hippolyte et al., 2009; Lanfranchi et al., 2010; Landry et al., 2012]. Simultaneous processing is a core underlying weakness relative to TD-MA matched children [Lanfranchi et al., 2004, 2009].

Self-Monitoring

Individuals with DS, from childhood through adulthood, have poor monitoring of their verbal comprehension or are unable to execute and create a plan to request clarification of instructions [Abbeduto et al., 1997, 2008]. Children, adolescents, and adults with DS often fail to signal that they do not understand [Abbeduto et al., 1997, 1998, 2008] and when compared with TD-MA matched controls, adolescents, and young adults with DS show lower frequency of signaling [Abbeduto et al., 2008]. Self-monitoring in adults remains vulnerable, as poor monitoring for intrusion errors and difficulty preventing irrelevant information from interfering with cognitive processing of relevant information has been demonstrated [Kittler et al., 2006].

Comparison Studies of EF

Overall, individuals with DS show impairments in EF that extend beyond those observed in individuals with ID of unknown etiology and of those with comparable MA [Rowe et al., 2006; Lanfranchi et al., 2010; Costanzo et al., 2013]. These deficits appear even in young children with DS [Gregory and Hodges, 1996]. Relative to young children with other genetic disorders associated with ID, children with DS show poorer sustained attention and verbal inhibition [Brown et al., 2003; Cornish et al., 2007; Porter et al., 2007;

Scherif and Steele, 2011]. Young children with DS also process information more slowly with more errors than children with Fragile X syndrome or Williams Syndrome [Cornish et al., 2007]. Children with DS show significantly more difficulty with shifting and verbal aspects of memory than children with Williams syndrome and TD-MA matched controls [Costanzo et al., 2013].

Individuals with DS show pervasive deficits across modality in working memory when compared with individuals with Williams syndrome and with TD children [Carney et al., 2013]. Working memory deficits in children and adolescents with DS were greater with regard to verbal stimuli [Lanfranchi et al., 2010]. On parent and teacher rating scales, young children with DS are reported to show significant deficits in aspects of EF [Lee et al., 2011] when compared with TD children matched for MA [Daunhauer et al., 2014]. Deficits observed are in working memory (nine times more likely than TD children to experience problems either at school or at home) and planning (six to seven times more likely to experience problems); parents also endorse significant problems with inhibitory control, whereas teachers do not [Daunhauer et al., 2014]. Individuals with DS show a pattern of global executive dysfunction, similar to that observed in individuals with Fragile X syndrome [Kirk et al., 2005; Hooper et al., 2008].

Visuo-Spatial Ability

In contrast to the commonly held view that nonverbal skills are a strength in individuals with DS, a recent review by Yang and colleagues [2014] found that nonverbal, visuospatial processing shows an uneven profile of skills, with some aspects of visuo-spatial abilities commensurate with general cognitive ability [Yang et al., 2014]; whereas, other aspects are below expected developmental level [Yang et al., 2014]. In some instances, visuo-spatial skills therefore remain an area of strength relative to weaker verbal skills and there is some evidence that visuo-spatial skills remain relatively preserved even in the face of cognitive decline [Jarrold et al., 1999; Fidler et al., 2006; Costanzo et al., 2013].

While early studies demonstrated deficits in nonverbal ability relative to matched MA peers [Meyers et al., 1961], more recent studies consistently show that visuospatial functioning (e.g., visual processing, visuospatial short-term memory, and visuoconstruction) develops to a level commensurate with MA [Wang and Bellugi 1994; Hodapp and Zigler, 1997; Jarrold et al., 1999; Klein and Mervis, 1999; Laws, 2002; Gathercole and Alloway, 2006; Kogan et al., 2009; Couzens et al., 2011]. Further analyses of trends within the visuo-spatial domain indicate that individuals with DS tend to approach visuo-spatial information using a global approach to analyzing information [Bellugi et al., 1999; Carretti et al., 2013]. When mistakes in nonverbal processing are made, they are often characterized by a failure to perceive, or to accurately perceive, details within the information [Bellugi et al., 1999; Carretti et al., 2013]. Of note, nonverbal processing is often compromised when greater integration and appreciation for more complex information is necessary, secondary to weakness in EF [Carretti et al., 2013].

When comparing children with DS and those with fragile X syndrome, individuals with DS show strength in spatial learning and object discrimination tasks, but have greater difficulty with visual-perceptual and visual-spatial reversal learning tasks [Kogan et al., 2009]. Similarly, children with DS have weakness in visual-perceptual abilities in the context of relatively preserved visual-spatial abilities when compared to children with Williams syndrome [Vicari et al., 2005]. These findings may reflect the aforementioned vulnerability in tasks with higher EF demands.

Learning

Individuals with DS show the capacity to learn and acquire new skills; however, the rate of learning and the range of skills acquired often differs from the trajectory of TD children and also from that of individuals with similar levels of intellectual functioning. Similar to many children with ID, children with DS show reduced learning capacities with regard to both short-term and long-term memory [Rast and Meltzoff, 1995; Carlesimo et al., 1997; Vicari et al., 2000, 2005; Brown et al., 2003; Clark and Wilson, 2003; Constestible et al., 2010]. Certain aspects of learning are identified as strengths. Children with DS perform favorably in paradigms of observational learning (observing the actions of others) [Reed et al., 2011] and when associating objects with rewards [Kogan et al., 2009]; whereas, they have greater difficulty with instrumental learning (manipulating the environment to meet their needs) [Wishart, 1993; Ohr and Fagen, 1994; Reed et al., 2011]. Their higher social motivation and responsiveness to positive reinforcement likely make socially oriented learning more successful. Visual learning is also stronger than verbal learning, a finding that is consistent with the strength in nonverbal ability relative to verbal ability characterized in the cognitive profile.

Long-term Memory

Individuals with DS have deficits on tasks of explicit verbal and nonverbal long-term memory [Carlesimo et al., 1997; Vicari et al., 2000; Nadel, 2003; Kogan et al., 2009]. Problems are believed to occur at the levels of encoding and retrieval [Carlesimo et al., 1997] and are adversely impacted by attention deficits [Brown et al., 2003; Clark and Wilson, 2003; Krinsky-McHale et al., 2008] and high processing demands [Lanfranchi et al., 2004; Rowe et al., 2006; Visu-Petra et al., 2007]. In addition, deficits in memory consolidation may exist secondary to temporal lobe and hippocampal dysfunction [Carlesimo et al., 1997; Pennington et al., 2003; Belichenko et al., 2004, 2009; Lott and Dierssen, 2010; Kleschevnikov et al., 2012]. Therefore, memory deficits may be primary in nature and do not exist solely as a manifestation of deficits in language

processing. These deficits exist across the lifespan [Ellis et al., 1989; Caltagirone et al., 1990], but become more pronounced with age.

SOCIAL/EMOTIONAL/ BEHAVIORAL FUNCTIONING

Individuals with DS are commonly perceived as "charming," "affectionate," "cheerful", and "sociable" with other observed personality assets that include kindness, humor, and forgiveness [Down, 1866; Dykens, 2007; Fidler et al., 2008]. These perceptions are founded in behavioral research. For example, children with DS seek out social interaction more frequently than children with nonspecific intellectual impairment and also demonstrate more positive facial expressions relative to typically developing peers [Kasari et al., 1995; Kasari and Sigman, 1996; Jahromi et al., 2008]. Relative to other children with ID, children with DS are at a lower risk for psychopathology [Dykens and Kasari, 1997; Stores et al., 1998] and families of children with DS report lower levels of stress [Hodapp and Dykens, 2004; Fidler et al., 2008] and a more positive outlook on life because of their child with Down syndrome [Skotko et al., 2011a].

Social development in DS appears to unfold in a similar fashion to that of a TD child; however, there are important qualitative differences in the development of emotional recognition, social referencing, joint attention, spontaneous gesturing, and lower levels of mastery motivation [Mundy et al., 1988; Kneips et al., 1994; Ruskin et al., 1994; Franco and Wishart, 1995; Legerstee and Weintraub, 1997; Glenn et al., 2001; Fidler et al., 2005; Cebula et al., 2010]. Strengths emerge in imitation abilities and in pro-social, empathic behaviors [Down 1866; Kasari et al., 2003]. While social motivation is a strength in many contexts, studies show that children with DS often use social distraction behaviors as a means of preventing the completion of a requested task [Pitcairn and Wishart, 1994; Kasari and Freeman, 2001]. Social distraction can occur subtly and is often not perceived as intentionally oppositional; however, as the behavioral regulation demands increase with a typical developmental trajectory, these behaviors become more apparent. Parents and teachers report a higher rate of noncompliance relative to siblings and TD children [Pueschel et al., 1991; Cuskelly and Dadds, 1992; Coe et al., 1999]. Poor task persistence and stubbornness are also commonly reported by caregivers and educators [Kasari and Freeman, 2001]. These latter personality characteristics, when present, relate to reduced levels of achievement when examined longitudinally [Gilmore and Cuskelly, 2009]. Task persistence that is observed early in childhood remains stable throughout childhood and into early adolescence [Gilmore and Cuskelly, 2009].

The research also shows higher rates of externalizing behaviors are commonly reported in early childhood and amongst school-aged children. For example, higher rates of hyperactivity, impulsivity, tantrums, agitation, stubbornness, disruptiveness/argumentativeness, repetitive movements, and sensory dysregulation are reported [Dykens and Kasari, 1997; Capone et al., 2006; Siegel and Smith, 2010]. For some individuals, disruptive behaviors may be secondary to deficits in expressive language communication [Skotko et al., 2013]. When comparing children with DS to those with nonspecific ID, greater and more intense displays of physical and vocal frustration are observed [Jahromi et al., 2008] and may relate to a disproportionate weakness in verbal expression. Compulsive behaviors are also a component of the behavioral phenotype of DS, evident more prominently in children with DS than other children with ID [Evans and Gray, 2000; Maatta et al., 2006].

As maturation occurs, individuals can experience higher rates of internalizing symptoms (e.g., social withdrawal, depression, anxiety, secretive behavior), whereas externalizing behaviors tend to decline [Cooper and Collacott, 1994; Evans and Gray, 2000; Dykens, 2007; Siegel and Smith, 2010]. Traits, such as a high level of social motivation, can begin to decline with age. For example, older individuals with DS show significantly fewer and briefer smiles than younger children [Fidler et al., 2005]. Fortunately, social reasoning skills amongst adults with DS remain relatively preserved [Hippolyte et al., 2010]. A survey of adolescents and adults with DS ($n = 284$) shows that 99% of the participants express feeling happy with their lives and express love for their families [Skotko et al., 2011b].

Many individuals are able to live in group settings with limited support, although studies show that most individuals remain in their family's home [Thomson et al., 1995; Pulsifer, 1996; Dyke et al., 2013; Foley et al., 2013]. Greater levels of functional independence have been found to predict participation in mainstream employment or occupational training when compared with individuals in sheltered employment or alternatives to employment situations [Foley et al., 2013]. It is important to note that parental advocacy and resourcefulness, as well as government policy and procedures, serve as mediating environmental factors that facilitate level of independence and opportunities [Dyke et al., 2013]. Relative to individuals with ID secondary to other genetic disorders, individuals with DS show fewer maladaptive behaviors [DiNuovo and Buono, 2011], consistent with older studies reporting fewer adaptive behavior problems [Dykens and Kasari, 1997; Chapman and Hesketh, 2000]. However, recent comparison shows that basic adaptive skills are reduced in individuals with DS than individuals with Prader–Willi, Fragile X, and Williams syndrome [DiNuovo and Buono, 2011].

While many adults with DS continue to function relatively well, depression is observed in higher rates than other individuals with ID in adulthood [Collacott et al., 1992; Maatta et al., 2006]. Psychiatric problems such as attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and self-injury behaviors may impact a considerable number of individuals with DS [Maatta et al., 2006; Siegel and Smith,

2010]. However, debilitating mental health conditions, including bipolar and schizophrenia, are relatively rare [Collacott et al., 1992; Craddock and Owen, 1994; Patti and Tsiouris, 2006]. In adulthood, the emergence and severity of psychological problems can be associated with the beginning stages of dementia [Haverman et al., 1994; Maatta et al., 2006; Dykens, 2007]. In fact, depression with apathy and withdrawal is believed to be a prodromal feature of dementia in DS [Burt et al., 1995] and marked changes in personality and behavior are early indicators of cognitive decline and dementia in the DS population [Nelson et al., 1995; Holland et al., 1998, 2000; Ball et al., 2008; Adams and Oliver, 2010]. Higher rates of depressed mood, restlessness, hyperactivity, sleep disturbance, excessive uncooperativeness and auditory hallucinations are observed with aging [Cooper and Prasher, 1998; Maatta et al., 2006; Dykens, 2007]. Cognitive deterioration, as well as co-morbid emotional and behavioral changes, commonly mandate more intensive supports [Pulsifer, 1996].

UNIQUE CHARACTERISTICS OF THE DOWN SYNDROME POPULATION

Dementia

Individuals with DS are at an increased risk for developing early-onset Alzheimer disease (AD), as this is associated with several genetic factors that are overexpressed on chromosome 21 [Lai and Williams, 1989; Evenhuis, 1990; Visser et al., 1997; Lott, 2012]: (1) overexpression of amyloid precursor protein resulting in B-amyloid plaques [Prasher et al., 1998; Bush and Beail, 2004; Constestabile et al., 2010; Krinsky and Silverman, 2013]; (2) degeneration of cholinergic neurons [Schliebs and Arendt, 2006; Kleschevnikov et al., 2012], and (3) disruption in the short-lasting biochemical synaptic events that serve to consolidate memory information [Lott and Dierssen, 2010]. AD occurs more frequently in individuals with DS than in other adults with ID [Zigman and Lott, 2007; Krinsky-McHale and Silverman, 2013]; however, prevalence rates of dementia amongst individuals with DS vary greatly in the literature (8–100%) [Zigman et al., 1996]. This variability is likely the manifestation of various sample characteristics within each study, the methodology used, and the time period in which the studies were conducted. While many individuals with DS are not impacted by dementia until after age 50 [Devenny et al., 1996, 2000; Roizen and Patterson, 2003; Couzens et al., 2011], by age 60 approximately 75% of individuals with DS experience symptoms of AD [Roizen and Patterson, 2003] and beyond age 60 there is often severe cognitive decline [Wisniewski et al., 1985; Lai and Williams, 1989; Chapman and Hesketh, 2000]. The incidence rates of initial diagnosis are also reported: $\leq$49 years = 8.9%; 50–54 years = 17.7%; 55–59 years = 32.1%; $\geq$60 = 25.6% [Coppus et al., 2006]. The average age of diagnosis of dementia is estimated to be around 55 years with a median survival rate of 7 years following diagnosis [McCarron et al., 2014]. Life expectancy has been extended to well over 60 years secondary to advancements in medical care [Glasson et al., 2002; Roizen and Patterson, 2003; Bittles and Glasson, 2004; Bittles et al., 2006; Constestabile et al., 2010]. Older age is identified as a strong risk factor to develop dementia; whereas, gender and severity of ID are not identified as predictors of developing dementia in DS [Krinsky-McHale and Silverman, 2013].

One of the main challenges in providing care for aging individuals with DS is the task of differentiating age-related decline from progressive cognitive decline associated with dementia. The vast majority of individuals with DS have neuropathological changes associated with AD; however, some do not exhibit symptoms of dementia [Chicoine et al., 1994; Devenny et al., 1996; Zigman et al., 1996; Oliver et al., 1998; Krinsky-McHale et al., 2002; Ball et al., 2006; Krinsky-McHale and Silverman, 2013]. Of those who are diagnosed with dementia, there is a variation amongst the first observable signs [Chicoine et al., 1994; Devenny et al., 1996; Zigman et al., 1996; Oliver et al., 1998; Krinsky-McHale et al., 2002; Ball et al., 2006; Krinsky-McHale and Silverman, 2013]. In some cases, impairments in EF are associated with the emergence of dementia [Rowe et al., 2006; Deb et al., 2007; Ball et al., 2008], particularly compromised attention and planning ability [Das et al., 1995]. Other symptoms associated with changes in the frontal lobes (apathy, depression, impaired adaptive functioning, and reduced communication) may indicate underlying neurodegeneration secondary to AD [Zigman et al., 1996; Lott and Head, 2001; Ball et al., 2006; Constestible et al., 2010].

Early detection of AD is associated with progressive impairment in selective attention as early as 2 years prior to a dementia diagnosis and it is generally accompanied by episodic memory loss [Krinsky-McHale et al., 2008]. Older studies propose impaired visual short-term memory as an early sign [Dalton and Crapper-McLachlan, 1986]; however, subsequent studies demonstrate deficits in this domain that are present throughout youth and adolescence [Lanfranchi et al., 2004; Rowe et al., 2006; Visu-Petra et al., 2007]; thus, this factor is not considered predictive. A clear differentiation between individuals with DS diagnosed with dementia and those without dementia is observed (mean age = 47 years), particularly in the cognitive domains of memory and EF even after controlling for age and degree of ID [Ball et al., 2008].

Sensory Impairment

Sensory impairments are commonly observed in individuals with DS and can adversely affect learning and cognitive functioning [Maatta et al., 2006]. It is estimated that between 38 and 78% of individuals with DS experience hearing loss and approximately 80% of children ages 5–12 years show vision problems, such as refractive errors, strabismus, and/or nystagums [Roizen and Patterson, 2003]. Augmentative supports and therapies are key components to supporting

cognitive development and functioning and are needed in higher frequency in the DS population.

Seizures

In individuals with DS, seizures occur at a higher rate than is observed in the general population [Roizen and Patterson, 2003] and often emerge during two main developmental periods: infancy and advanced age. Infantile spasms are the most commonly observed type of seizure [Lott, 2012] and may persist into early childhood; it is estimated that 5–13% of children with DS have co-morbid seizures [Arya et al., 2011; Lujic et al., 2011; Lott, 2012]. These events can be particularly detrimental, especially when they occur frequently, as they can disrupt neuronal development and subsequently contribute to further delays or disruptions in development. In later adulthood, generalized seizures typically emerge in the context of cognitive decline and cortical atrophy [Lott, 2012]. The emphasis in this phase shifts to concern surrounding a loss of functional skills and the advanced decline of cognitive functioning [Lott and Dierssen, 2010].

Sleep Disruption

Many individuals with DS experience high rates of sleep problems, including obstructive sleep apnea, reduced REM sleep, and poor sleep initiation and maintenance [Stores et al., 1998; Harvey and Kennedy, 2002; Dykens, 2007; Capone et al., 2013]. These difficulties are associated with significantly poorer performance on tasks of attention and EF [Beebe and Gozal, 2002; Chen et al., 2013; Breslin et al., 2014], as well as memory storage/consolidation [Breslin et al., 2014], and may exist in the context of co-morbid depression [Capone et al., 2013]. Proper sleep hygiene and interventions are an essential component to optimizing cognitive functioning.

Autism Spectrum Disorder

Approximately 6–10% of children have co-morbid autism spectrum disorder (ASD) [Kent et al., 1999; Lowenthal et al., 2007; Molloy et al., 2009; Siegel and Smith, 2010], which possesses its own set of unique challenges. Diagnosing a behavioral disorder, such as ASD, is difficult to define in the DS population due to the behavioral diagnostic criteria of the syndrome that may overlap with phenotypical social communication patterns associated with DS [Reilly, 2009]. However, when co-morbid diagnosis is clearly present, children are often more severely cognitively impaired and show greater delay in the development of language and adaptive behavior skills [Capone et al., 2005; Molloy et al., 2009]. Additionally, dual-diagnosis is marked by a distinctive pattern of unusual stereotypic behavior, anxiety, and social withdrawal [Carter et al., 2007]. Together, these factors result in reduced levels of functional independence.

Other Common Medical Factors

Additional conditions with higher incidence within this population include celiac disease, hypothyroidism, leukemia, congenital heart defects, and diabetes [Roizen and Patterson, 2003; Visootsak et al., 2011; Lott, 2012]. Left untreated, these conditions may result in changes in cognition, behavior, and energy level. Underdetection is common, as a recent study showed that only 9.8% of patients with DS were clinically up to date on the recommended screenings from the American Academy of Pediatrics [Skotko et al., 2013]. Attention to and proper screening for a common co-morbid condition are warranted.

DISCUSSION

The literature of cognitive and behavioral functioning of individuals with DS reveals a pattern of development that is characterized by unique strengths and weaknesses that emerge in stages throughout the progression of the lifespan. Key features of the DS phenotype include relative strengths in nonverbal abilities and social motivation. In contrast, weaknesses in language are consistently observed, with expressive language, syntax, articulation, phonological processes, and verbal working memory as the most vulnerable areas of functioning. Variable functioning across aspects of EF are observed. Optimal performance is evident on succinct, concrete tasks supported by explicit multisensory presentation. Weaknesses emerge as the complexity, length, and demands for integration increase, regardless of the modality in which the information is presented. Co-morbid factors described above (e.g., sensory impairment, sleep disruption, etc.) can further contribute to cognitive and behavioral difficulties and must be recognized when examining functioning.

Specific patterns of cognition are also demonstrated across the lifespan both relative to matched MA-TD peers and to individuals with various genetic syndromes associated with ID. Interestingly, examination of cognition in individuals with DS is unique and differs from both of the aforementioned groups. The results from these studies provide support for the observation of a unique cognitive phenotype for individuals with DS that is distinct from other individuals even with matched level of cognitive functioning. It is important to consider the demands of the tasks when designing studies and interpreting results of others' studies in relation to specific cognitive phenotypes, such as a relative weaknesses in language processing for individuals in the DS population as such confounding factors may inaccurately influence our interpretations [Channell et al., 2014b]. Importantly, recent neuroimaging and functional imaging studies (that are briefly described here) have demonstrated both structural and functional correlates consistent with the defined cognitive pattern providing support for the unique phenotypic patterns observed across the lifespan.

Cognitive functioning directly informs the ability to learn academic skills, as well as to apply knowledge to novel information to function independently. Individuals with DS are highly socially motivated and show strengths in observational learning and nonverbal

capabilities. However, many individuals with DS remain limited in their ability to function independently [Maatta et al., 2006]. As such, functional living skills should be incorporated in school curriculum at an early age to support the development of these skills. The role of social, behavioral, and emotional functioning must also be considered. Commonly observed strengths and challenges that are depicted within each developmental period should be assessed. The provision of behavioral and emotional supports and opportunities for socialization may improve overall level of independence and self-care skill development, and enhance overall quality of life.

Intervention to improve functioning and slow decline are underway and several different approaches such as pharmacological treatments [Capone, 2010; Costa, 2011; De la Torre and Dierssen, 2012; Kleschevnikov et al., 2012], complementary and alternative therapies and therapeutics diets [Salman, 2002; Roizen, 2005], and cognitive rehabilitation strategies are being examined [Broadley and MacDonald, 1993; Comblain, 1994; Messer and Hasan, 1994; Laws et al., 1996; Conners et al., 2008]. The application of behavioral strategies, particularly applied behavior analysis techniques, also shows favorable results by increasing on-task learning behaviors and reducing challenging behaviors in order to support learning [Feelin and Jones, 2005].

Considerations when interpreting the information outlined above include the need for caution when applying this phenotypic pattern to all individuals with DS, as the pattern is not intended to define each individual's unique strengths and weaknesses. Alternatively, it should be used as a framework from which to guide assessment and inform interventions. When interpreting these studies, one must also appreciate the relationship between performance and competence. Many individuals do not consistently demonstrate their full capacities on formal testing and therefore results may not reflect their true level of ability [Wishart and Duffy, 1990; Wishart, 1995; Silverman, 2007]. Another factor is the variability among the composition of participants within each study, the methodology used to examine functioning, and the limitations in reliability and validity of the tools used to quantify abilities.

In conclusion, appreciating the unique cognitive and behavioral phenotypes associated with DS will help professionals and parents understand individuals with DS more fully, as well as inform treatments and instructional methods for learning. Improved conceptualization of areas of strengths and weaknesses will help professionals and families support the growth of the individual with DS to their highest level of independence, ultimately optimizing their functioning and quality of life.

Conflict of Interest

Margaret Pulsifer, Ph.D, services in a non-paid capacity on the Board of Directors for the Massachusetts Down Syndrome Congress, a non-profit organization. Brian Skotko, M.D, MPP, serves in a non-paid capacity on the Board of Directors or Scientific Advisory Boards for the Massachusetts Down Syndrome Congress, Band of Angels Foundation, and the National Center for Prenatal and Postnatal Down Syndrome Resources, all non-profit organizations. Dr. Skotko is the Co-Director of the Massachusetts General Hospital Down Syndrome Program and occasionally gets remunerated from Down syndrome non-profit organizations for speaking engagements about Down syndrome. He receives support for clinical drug trials involving people with Down syndrome from Hoffmann-La Roche, Inc. He has a sister with Down syndrome. Authors Julie Grieco, PsyD, Karen Seligsohn, Ph.D, and Allison Schwartz, M.D, have no actual or potential conflicts of interest to report.

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