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Prenatal and Postnatal Pharmacotherapy in Down Syndrome: The Search to Prevent or Ameliorate Neurodevelopmental and Neurodegenerative Disorders

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Abstract

Those with Down syndrome (DS)—trisomy for chromosome 21—are routinely impacted by cognitive dysfunction and behavioral challenges in children and adults and Alzheimer's disease in older adults. No proven treatments specifically address these cognitive or behavioral changes. However, advances in the establishment of rodent models and human cell models promise to support development of such treatments. A research agenda that emphasizes the identification of overexpressed genes that contribute demonstrably to abnormalities in cognition and behavior in model systems constitutes a rational next step. Normalizing expression of such genes may usher in an era of successful treatments applicable across the life span for those with DS.

Keywords

Down syndrome; intellectual disability; neurogenesis alterations; connectivity alterations; neurodegeneration; pharmacotherapy

INTRODUCTION: AN ONCOMING ERA OF TREATMENTS FOR DOWN SYNDROME

Extraordinary advances have addressed care for those with Down syndrome (DS) or trisomy 21 and have defined how this most common aneuploidy impacts growth, development, and aging. Described by John Langdon Down in 1866 (1), the chromosomal basis was defined in 1959 (2, 3), and the condition was named Down's syndrome in 1961 (4). One in every 792 live-born infants in the United States is diagnosed with DS (5); at present,

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approximately 200,000 individuals with DS live in the United States. DS is often diagnosed in the postnatal period through detection of changes in the facies, limbs, and muscular hypotonia. Chromosome 21 (HSA21) encodes an estimated 233 protein-coding genes, 423 non-protein-coding genes, and 188 pseudogenes (6). Trisomy of HSA21 results in increased expression of many genes on HSA21 as well as other chromosomes, leading to characteristic phenotypes. Those with DS are variably affected by congenital heart disease, disorders of the digestive tract, hematologic disorders including leukemia, hypothyroidism, sleep disorders, and disorders of hearing and vision (7). Cognitive dysfunction is universal and typically moderate to severe (8–10). Recent decades have ushered in striking demographic changes. Surgical correction of congenital heart defects and provision of routine care has increased longevity from a median of 25 years in 1983 to 60 years in 2013 (11–13). Increased longevity has resulted in an increase in age-related disorders and medical comorbidities, the most important of which is Alzheimer's disease (AD) (9, 14).

There is no syndrome-modifying treatment for cognitive disorders in children or adults with DS. However, new methods and disease models are enabling studies deciphering the genetic, molecular, and cellular bases for cognitive dysfunction. Accordingly, defining treatment targets and discovering interventions has taken on increasing importance. Herein we provide an overview of evidence regarding cognitive dysfunction in infants, children, and adults with DS and highlight translational efforts and opportunities. A path to developing therapeutics for DS is emerging. As guideposts, we note that (*a*) all manifestations in DS are due to the presence of an extra copy of one or more genes or regulatory elements on HSA21; (*b*) the resulting changes in the genetic environment are complex; (*c*) environmental factors, including aging, interact with genetic changes; and (*d*) changes in the developing brain have lifelong effects. An important additional guidepost to future treatments is that the DS population demonstrates considerable variability with respect to cognitive skills and behavioral manifestations. This may necessitate creating trial cohorts informed by and that control for baseline function. Although complexity frustrates discovery of treatments, a research agenda that identifies genes whose overexpression contributes demonstrably to abnormalities in cognition and behavior constitutes a rational first step, one that has already proved feasible. We argue that treatments to normalize expression of such genes, the activity of their products and the cellular pathways in which they participate, or both may usher in an era of successful treatments for those with DS.

THE PRENATAL PERIOD: CHANGES IN THE DEVELOPING DOWN SYNDROME BRAIN

Widespread Changes in Prenatal Brain Development in Down Syndrome

The onset of cognitive and behavioral dysfunction in DS begins in utero with deviations from normal registered during early brain development. There is an overall reduction in brain volume, particularly the cerebellum, brainstem, and hippocampus, with concomitant changes in cell number, migration, and differentiation (15, 16). Excitatory cortical neurons and glial cells originate in the ventricular and subventricular zones and migrate to their final destination, where they take on their mature structure and function (differentiation) (17). Interneurons are generated in the medial and caudal ganglionic eminence before

migrating tangentially to the cortex (18). Neurogenesis comprises (*a*) cell generation from neural progenitor cells (NPCs), (*b*) acquisition of either a neuronal or glial phenotype, and (*c*) programmed cell death (apoptosis). The migration of young neurons and glial cells establishes the regional architecture. Once migrated, neurons complete differentiation through development of dendrites and axons and establishment of synaptic connections; in some neurons, dendritic spines are the loci of synapses. Myelin wrapping of large axons enhances conduction of action potentials. Deviations in each of these processes are evident in the developing DS brain.

Cell generation.—At gestational weeks 17–23, cell proliferation is notably reduced in DS fetuses (−17% to −69% versus control fetuses) in the ventricular and subventricular zones, hippocampal areas, and cerebellum (see 15, 16). Complementing this evidence, in vitro studies show impaired proliferation in neurospheres generated from the cortex of DS fetuses and NPCs obtained from human induced pluripotent stem cells (hiPSCs) from individuals with DS (19, 20; see also 16). Intriguingly, an increase in interneuron neurogenesis has been detected in DS hiPSC brain organoids (21), consistent with evidence in a model of DS (22).

Cell number and phenotype acquisition.—Consistent with impaired proliferation, reduced cell number was detected in the neocortex, hippocampal region, cerebellum (see 16), and thalamus (23) of DS fetuses (−22% to −39%). Moreover, a reduction in neurons and a higher proportion of cells with astroglial and oligodendroglial phenotypes was detected in fetal DS brains (24, 25) and cultures of NPCs derived from DS fetuses or DS hiPSCs (19, 25–28).

Apoptotic cell death.—There are discordant findings on apoptotic cell death in fetal DS brains and cultures of DS NPCs (20, 29; see also 15).

Cortical lamination.—Lamination is delayed and disorganized, particularly regarding superficial layers (30; see also 15). Defects in GABAergic neuron migration (31) may contribute to abnormal cortical layering.

Dendritogenesis and spinogenesis.—Dendritic hypotrophy first appears at 3–4 months of postnatal age (32, 33). Likewise, differentiating neurons from fetal DS brains or DS hiPSCs exhibit a reduction in neurite length and number (19, 20, 27, 28). Cortical neurons of DS fetuses have a similar number of spines as those of control fetuses, but in newborns and older infants there are fewer spines and spines with altered morphology (32).

Axon myelination.—No myelination defects have been detected in DS fetuses. In infants with DS, however, myelination is delayed starting from one month of age, and a reduction in the density of myelinated fibers becomes more evident with age (34).

Conclusions.—In summary, the fetal DS brain reveals deviations from normal in the developmental events responsible for brain growth and functioning. Taken together, the changes are consistent with intellectual disability in infants with DS and with cognitive and behavioral changes in later infancy and adolescence.

The Prenatal Period: Gaps, Resources, and Approaches for Treatments

Treatments that restore normal brain development may have lifelong effects. To discover them, research must address two fundamental gaps. The first is the absence of a comprehensive and detailed view of the events that constitute disordered DS brain development. The second is evidence for which genes present in excess on HSA21 contribute to this disordered development and the underlying mechanisms they induce. Thus, additional studies in the human fetal brain and in model systems will be essential. In spite of limited knowledge and changes in many processes, neurogenesis emerges as a first important target whose contribution to cognition is fundamental. Thus, studies focused on the genes and mechanisms that contribute to changes in neurogenesis deserve emphasis.

Studies of the fetal Down syndrome brain.—Limited availability of fetal material has resulted in neurogenesis studies using small numbers of samples, developmental time points, or both. An important goal would be creation of a robust, shared biobank of fetal brains [similar to the US National Institutes of Health NeuroBioBank (https://neurobiobank.nih.gov/)], supported by clinical data and using standardized protocols for documenting brain development. The research agenda would focus on temporospatial patterns of neurogenesis and gliogenesis. Single-nucleus sequencing methods could be used to define neuronal and glial subtypes, probe changes in gene expression in identified subpopulations, and identify dysregulated pathways. Recent advances promise important insights (35). Indeed, studies of this type could be a first step to articulating a rationale for a prenatal treatment or treatments to rescue neurogenesis and the neurogenesis/gliogenesis balance. Importantly, real-time imaging of the in utero DS brain is possible via MRI techniques (36). MRI may prove useful for defining the time course and distribution of changes in brain anatomy and, indirectly, for monitoring treatments to restore neurogenesis and brain growth.

Down syndrome models.—Studies in fetal tissue will benefit from continuing studies in animal and human models of DS.

Mouse models.: A large number of mouse models of DS have been created (37). The mouse genome contains segments on chromosome 16 (Mmu16), Mmu17, and Mmu10 that harbor genes also present on the long arm of HSA21. To a variable degree, specific models exhibit traits similar to those in DS. The Ts65Dn mouse was the first readily available model; its genome contains about 90 protein-coding genes orthologous to the human genes. This segment is fused with the Mmu17 centromere and is thus present in a freely segregating chromosome. This is the most used model. A limitation is that it carries an extra copy of Mmu17 genes not shared with HSA21. This and other models have an imperfect match between human and mouse genes within syntenic segments. Chromosomal engineering has enabled researchers to target specific segments for duplication or deletion, thus facilitating production of many of the models now in use to discover genotype-phenotype correlations. Transgenic models overexpressing HSA21 genes have been examined; possible limitations are nonphysiological levels of expression and the absence of other trisomic genes. Despite limitations, genotype-phenotype insights for DS largely come from mouse models, which enable studies across the life span and the ability to incisively interrogate genes and

mechanisms. With these models, researchers have made progress in deciphering the impact of triplicated genes on neurogenesis and gliogenesis, cellularity, functionality of cellular pathways, neuronal function, and cognition. Importantly, the models have enabled studies of several pharmacological agents on DS brain phenotypes and cognitive performance. The result is an increasingly rational basis for the design of clinical trials in individuals with DS. Continued development of models is expected, such as the TcMAC21 mouse that harbors a copy of freely segregating HSA21 (38). Unfortunately, in comparison to postnatal studies (see 39–44), to date, few studies in mouse models examined treatment during the prenatal period (45, 46; see also 40).

Human cell models.: Postmortem brains provide a snapshot of cellular and molecular events but not a view of developmental dynamics. The use of 2D and 3D in vitro models of NPCs derived from DS fetuses or DS hiPSCs helps to overcome these limitations (47) and has confirmed changes in neurogenesis and gliogenesis observed in fetal material (19, 20, 25, 27, 28, 48). The use of co-cultures comprising neurons, astrocytes, and oligodendrocytes (49) will be needed to understand the interactions between different cell types. Human cerebral organoids derived from hiPSCs may also serve to model brain development (50, 51), and ongoing unpublished and published (21) studies suggest that DS organoids will be informative. Limitations of organoids include the omission of oligodendroglia and microglial cells and absence of a vasculature to support nutrient delivery (47). Advances are being made to address such limitations (51). A model consisting of tissue grafts of NPCs generated from DS hiPSCs implanted into the mouse brain may represent an additional platform to capture developmental dynamics (52). Finally, the discovery that neurogenesis can be improved in DS patient–derived neural stem cells by silencing one of the three HSA21 chromosomes through insertion of the *XIST* gene (53) points to additional future possibilities for prenatal treatment to increase neurogenesis as well as, possibly, other manifestations of brain development.

Genes and Mechanisms: Current Insights

The large number of triplicated genes and the fact that triplication of chromosome 21 may transactivate (or transinhibit) genes on other chromosomes makes it difficult to identify the genes that impair brain development. Yet knowledge of the role of some of the triplicated genes in the healthy brain, corroborated by evidence in DS models, has highlighted some very likely culprits, among which some strong candidates are evident. At the forefront, reduction in proliferation of neuronal precursors points to the *DYRK1A*, *APP*, *RCAN1*, and *OLIG1/2* genes (Figure 1a). For each, over-expression leads to deregulation of cell cycle regulatory factors and premature exit from the cell cycle (20, 25; see also 16, 54). *APP*, *IFNAR1/2*, *IFNGR2*, *IL10RB*, and *DYRK1A* are candidates for neurogenesis impairment and gliogenic shift in DS NPCs through overactivation of the JAK-STAT pathway (see 16, 55). Countering neurogenesis, increased apoptosis may be attributable to overexpression of *ETS2*, *S100beta*, *APP*, *SOD1*, *RCAN1*, and *PREP1*; each can increase the activity or transcription of proapoptotic factors (see 16).

Envisioning a Path for Discovering Targets for Treating Developmental Abnormalities in Down Syndrome

Existing insights and models are sufficient to suggest a path to counter abnormalities in brain structure and function, with a focus on neurogenesis. Although the genetic environment of DS is complex, it is nevertheless true that overexpression of individual genes may powerfully impact phenotypes. With this in mind, one can ask which such genes can be identified as necessary for failed neurogenesis. Among those candidates listed above, *DYRK1A* is the most explored in animal models and clinical trials because it appears to be a key determinant of neurogenesis failure (see 56). Thus, compounds that inhibit DYRK1A kinase activity may prove effective. Indeed, treatment with epigallocatechin gallate (EGCG), a natural (although not selective) inhibitor of DYRK1A (57), ameliorated postnatal neurogenesis and behavior in Ts65Dn mice, but these effects did not extend beyond cessation of treatment (58). Although inconsistent findings question the beneficial effects of EGCG, evidence that ALGERNON, a synthetic DYRK1A inhibitor, restores corticogenesis in Ts1Cje embryos (45) has prompted further efforts. Accordingly, we can recommend a research agenda under which (*a*) an intensive focus on neurogenesis in mouse and human model systems defines the contribution of *DYRK1A*; (*b*) once confirmed, the same models are used to test existing and novel reagents for restoring neurogenesis, including small-molecule inhibitors and novel RNA-focused technologies [e.g., small interfering RNA (siRNA)]; (*c*) in DS mouse models, the optimal dose(s) and prenatal time(s) for treatment are defined and downstream effects on brain development are examined, as are adverse effects in the fetus and mother; and (*d*) the most promising treatments are advanced to trials. A campaign to counter defective neurogenesis promises to enhance brain development.

Ethical Considerations Concerning Prenatal Treatment

Current research increasingly supports the feasibility of clinical trials in people with DS. Through noninvasive prenatal testing, it is possible to identify fetuses with DS, thereby enabling trials during pregnancy. Significant ethical concerns, however, are raised. Is it ethical to treat a person during the fetal period? Considering the fetus as vulnerable, therapies would be ethically justified only if there are no caveats in terms of safety (e.g., teratogenicity and toxicity), they have evidence to support possible efficacy with respect to improved health and quality of life of the treated person, and they are safe and tolerable for the mother. But who represents the fetus in a decision as to whether a treatment is given? Is it only the parents, or is there a need for an appointed representative for the fetus? Is it ethical to give pregnant persons a treatment from which they do not benefit directly? These and other questions deserve a robust discussion. Although there is much to learn about the benefits that could attend prenatal treatment, we believe the time is ripe for assembling a wide-ranging discussion on the ethics that engages the DS community, researchers who study DS, ethicists, and society as a whole, the latter as represented by governmental agencies.

THE DOWN SYNDROME BRAIN IN CHILDHOOD AND YOUNG ADULTHOOD

Cognitive Functions and Psychiatric Comorbidity in Children and Young Adults with Down Syndrome

Over the past 75 years, the neurocognitive development and function of individuals with DS has been much researched. Tables 1 and 2 summarize key features in children and young adults with DS. Differences in short- and long-term memory, attention, cognitive flexibility, language, and behavior distinguish those with DS from both typically developing children and adults as well as those with conditions that feature intellectual disabilities. The changes are correlated with widespread brain abnormalities, decreased total brain volume, decreased hippocampal and cerebellar volumes, and decreased total gray and white matter in several cortical regions (59). These changes are linked to synaptic dysfunction and result in abnormal functional connectivity (60) and function of circuits that underlie them. Establishing robust linkages between clinical phenotypes and circuit function are essential for progress in defining molecular and cellular mechanisms and for discovering treatments.

Rationale for Targeted Therapies for Cognitive Functions

Cognitive pharmacotherapy in DS is in an early stage of development; as yet, no approach has demonstrated significant clinical benefit. Unfortunately, in many cases, the rationale for treatments was underdeveloped, the number of subjects limited, and the outcome measures neither sensitive nor specific to changes in DS. The question arises, What approaches would prove successful in children and young adults? Pathophysiological mechanisms responsible for clinically meaningful phenotypes should be prioritized. With neurogenesis being a prenatal event, albeit with continued activity in the hippocampus and regions producing neurons destined to the olfactory bulb postnatally, and given completion of neuronal migration, approaches focusing on enhancing neuronal differentiation and synapse formation are most attractive. Indeed, synapse maturation and axonal myelination are largely postnatal events, with dynamic changes in synaptic function across the life span. Which synapse-related genes and mechanisms should be prioritized? Recent reviews of studies in postnatal models point to several possibilities (39, 41–44, 56). One is *DYRK1A*, whose many substrates and related functions suggest a possibly pivotal role in synapse function (56) (Figure 1b). Thus, therapies targeting reduced expression and actions of this gene may prove useful. Other possibilities are also attractive as targets for postnatal therapy. As suggested for prenatal treatments, a focus on HSA21 genes whose overexpression is necessary for defined neuronal phenotypes may serve as a productive point of departure.

Evidence from Preclinical and Clinical Studies

Preclinical and clinical studies suggest that treatments targeting *DYRK1A*, neurogenesis, and neurotransmitter systems may exert beneficial effects on cognitive functions in DS.

Treatments targeting *DYRK1A*.—Normalizing *Dyrk1A* gene dose in the Ts65Dn and Dp16 mouse models improved working memory and contextual fear memory and restored hippocampal long-term potentiation (LTP), a cellular measure of learning and memory (72, 73). Numerous chemical candidates target different aspects of *DYRK1A* function: harmine, EGCG, INDY, BINDY, FINDY, Leucettine L41, and ALGERNON (see 56, 74). EGCG,

a catechin present in green tea that noncompetitively inhibits DYRK1A kinase activity, was used to treat newborn Ts65Dn mice, resulting in increased postnatal neurogenesis and increased immunoreactivity of synaptic proteins (synaptophysin and PSD95) in the cortex and hippocampus, restoring these parameters to normal (58). In young adult Ts65Dn mice (3 months old), EGCG added to drinking water for 30 days improved spatial memory and object recognition memory (75). However, using the same EGCG dose and treating younger mice (age 28 days) for 44 days failed to demonstrate benefit in these tasks and was linked to detrimental effects on the skeleton (76). A pilot irrefutable trial carried out in young adults with DS assigned participants to either EGCG ($n = 13$) or placebo ($n = 16$). Treatment for 3 months showed improvement in visual memory (75). De la Torre and colleagues (77) conducted a follow-up Phase II study in young adults with DS randomly assigned to a double-blind, placebo-controlled trial comparing EGCG plus cognitive training ($n = 43$) to placebo plus cognitive training ($n = 41$). The EGCG plus training group was significantly different from placebo at 12 months in tests of (*a*) immediate visual memory {adjusted mean differences of changes from baseline between treatments = 6.23 [95% confidence interval (CI), 0.31–12.14], a change of 6.23% with respect to the full scale score}, (*b*) executive function (i.e., inhibitory control) [adjusted mean differences of changes from baseline between treatments = 0.48 (95% CI, 0.02–0.93), a change of 3% with respect to the full scale score], and (*c*) adaptive behavior (i.e., functional academic skills) [adjusted mean differences of changes from baseline between treatments = 5.49 (95% CI, 2.13–8.86), a change of 7% with respect to the full scale score). The changes were thus quite modest; moreover, the effects were seen in only a minority of the measures evaluated. Treatment was safe and well tolerated (77). Interpretation of improvements is confounded by the fact that EGCG was combined with cognitive training. Perhaps an even more significant limitation to interpreting the results is that the actions of EGCG are known to extend beyond DYRK1A. Additional studies in mice and humans will be needed to demonstrate safety and efficacy, ideally using more specific and potent inhibitors of DYRK1A. Nevertheless, current findings support the potential value of these efforts.

Treatments targeting postnatal neurogenesis.—Administration of P7C3 (an aminopropyl carbazole) (78), fluoxetine, or lithium has been shown to restore postnatal neurogenesis and cognitive performance in Ts65Dn mice (79). Both fluoxetine and lithium have been approved for other indications in humans, and a clinical trial using fluoxetine is ongoing in DS (EudraCT number 2011-001556-11).

Treatments targeting neurotransmission.—Based on evidence that the DS brain exhibits aberrant functioning of the GABAergic, glutamatergic, and cholinergic systems, some studies have sought to establish whether pharmacological manipulation of these systems translates into a behavioral benefit.

GABAergic system.: Studies in the Ts65Dn and other mouse models point to increased GABAergic neurotransmission as being responsible for failed LTP (80). Administration of nonselective $GABA_A$ antagonists such as pentylenetetrazole (PTZ) rescued deficits in LTP and memory in the Ts65Dn mouse (81–83). Although the anxiogenic and proconvulsant effects of PTZ do not favor its use in clinical trials, a clinical trial

(ACTRN12612000652875) of the drug was carried out in adolescents and young adults with DS (13–35 years old) to assess cognitive and behavioral abilities before and after treatment; the results are not yet published. Administration of a selective negative allosteric modulator (NAM) of the α5IA subunit of the $GABA_A$ receptor restored hippocampal synaptic plasticity, restored spatial learning, and increased hippocampal neurogenesis in Ts65Dn mice (84). Basmisanil, an NAM of the $GABA_A$ α5 receptor, was tested in a double-blind, placebo-controlled study (NCT020224789). No significant effects were observed in cognition or adaptive behaviors (42). In Ts65Dn mice, there is evidence for $GABA_A$ receptor–mediated excitation, instead of inhibition, due to alterations of Na-K-Cl cotransporter 1 (NKCC1). Bumetanide, an NKCC1 inhibitor, suppressed $GABA_A$ receptor–mediated excitatory currents and rescued LTP and memory deficits (85). A clinical trial of bumetanide is ongoing in children and adolescents with DS (EudraCT number 2015-005780-16). Studies on $GABA_B$ receptor signaling in Ts65Dn mice showed increased signaling and that reagents that antagonized $GABA_B$-mediated inhibition restored synaptic plasticity and long-term memory (81). Increased $GABA_B$ receptor signaling could be due to increased activation downstream from the Kir3.2 (Girk2) subunit–containing potassium channels. Kir3.2 subunits are encoded by *Kcnj6*, a gene present on HSA21. Genetic normalization of *Kcnj6* copy number rescued hippocampal LTP and long-term memory (86). Treatments directed at GABAergic neurotransmission hold promise, as would those that selectively target reduction in KCNJ6.

Glutamatergic system.: Approaches to glutamatergic transmission have focused on the *N*-methyl-D-aspartate (NMDA) receptor. Treatment with the NMDA receptor antagonist memantine improved several measures linked to cognition in the Ts65Dn mouse (39, 87). A pilot study in young adults with DS showed that memantine was well tolerated and resulted in partial learning improvement (88). A follow-up clinical study is underway to assess the effects of memantine in adolescents and young adults with DS (NCT02304302).

Cholinergic system.: Although cholinergic neurotransmission plays a role in learning and memory (89), relatively few studies have tested cholinergic agents in models of DS (see 39). In clinical trials, Heller and colleagues (90, 91) carried out a nonrandomized, open-label, 20-week, pilot clinical trial of rivastigmine, a cholinesterase inhibitor, in 11 children with DS. There were significant improvements in expressive language and certain measures of memory and attention (90), but no significant improvements were found in participants who elected to receive rivastigmine long-term versus those who elected to stop the drug after the initial period of study (91). A 12-week, randomized, double-blind, placebo-controlled study of donepezil, another cholinesterase inhibitor, was conducted in 123 young adults (age 18–35 years) with DS. Scores on the primary outcome measure of cognition improved significantly from baseline in both donepezil and control groups, with no significant difference between them (92). A 10-week, randomized, double-blind, placebo-controlled, multicenter study assessed the efficacy and safety of donepezil in 129 children with DS (age 10–17 years) with mild to moderate cognitive severity, examining several measures of cognitive function and behavior. No treatment benefits were detected (93). There is currently no support for treatments to increase acetylcholine levels in children and young adults with DS.

Treatments targeting oxidative stress.—Studies in the Ts65Dn mouse demonstrated that supplementation with α-tocopherol or vitamin E ameliorated oxidative stress and induced cognitive improvements (94). Lockrow and colleagues (95) treated young adult Ts65Dn mice with α-tocopherol and observed improved spatial working memory and attenuated pathology involving septal cholinergic neurons. Studies employing α-tocopherol and antioxidants have failed to report significant cognitive benefits in children or young adults with DS (see 96). Infants with DS younger than 7 months in age were enrolled in an 18-month-long trial in which diets were supplemented daily with antioxidants, including α-tocopherol. There was no beneficial effect on psychomotor development or language acquisition. The addition of folinic acid had no effect on outcomes. To date, no clinical benefit has attended targeting increased oxidative stress in either children or adults. Future studies may benefit from attempts to define sources of oxidative stress and treatments to specifically address them.

Therapeutic Targets for Psychiatric Comorbidity

Psychiatric disorders may co-occur with intellectual disability. Since they are not necessarily linked to intellectual disability, these conditions are regarded as treatable.

Overview and rationale.—Changes in mood and behavior are common in people with DS, in many cases causing concerns for parents and caregivers (97). Defining changes in synaptic structure in circuits active in mood regulation would support treatment advances. However, few DS mouse model studies addressed changes in behavior and mood and their response to treatment (see 37).

As for studies in models, the marked prevalence of psychiatric comorbidities stands in distinction to the paucity of research focused on psychopharmacological treatments for DS. Indeed, available evidence consists primarily of case reports and case series. Only two randomized controlled trials on behavior and mood in DS have been published (98, 99).

Evidence from clinical studies.—Clinical studies show that attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), mood disorders, psychosis, and regression are psychiatric comorbidities with a relatively high prevalence in DS.

Attention deficit hyperactivity disorder.: The prevalence range of ADHD in DS is 31–43.9% (100). Capone and colleagues (99) provided evidence for the efficacy of guanfacine in reducing ADHD symptoms in children with DS. Considering the prevalence of ADHD symptomatology and its impact on daily functioning, additional studies of candidate medications for the DS population are needed.

Autism spectrum disorder.: The prevalence range of ASD in DS is 7–19% (101). Diagnosing ASD in children with DS, in whom some typical behaviors overlap with those for ASD, such as repetitive behaviors, can be challenging. Available evidence shows that treatment with risperidone reduces disruptive behaviors and self-injuries (98).

Mood disorders.: The prevalence of mood disorders in DS ranges from 0% to 11% (102, 103). Reduced interest appears to be the most frequently reported symptom of depression in adults (104, 105). Evidence shows that antidepressants and electroconvulsive therapy for adolescents and young adults with DS are effective (106). No study has addressed pharmacotherapy for bipolar disorders in young people with DS.

Psychosis.: Dykens and colleagues (71) reported a prevalence of psychosis of 35% in a sample of adolescents and young adults with DS, noting that psychosis was seen mostly in females. Case reports and case series report that the use of typical antipsychotics in DS is usually effective, albeit with concerns regarding tolerability. In particular, amitriptyline was reported to be helpful (106).

Regression.: Regression is a relatively recent diagnostic consideration and refers to a condition characterized by reduced speech and psychomotor activity and a loss of autonomy and daily skills with mean age of onset in the late teen years (107). There is little evidence supporting treatments for regression and catatonia; some preliminary findings suggest a possible role of immunotherapy in symptom amelioration (106, 108). Moreover, use of psychopharmacotherapy is attended by the risk of side effects and safety concerns. Additional studies to define safe and effective treatments are needed.

Envisioning a Path for Discovering Targets for Treating Cognitive and Behavioral Abnormalities in Down Syndrome

Noting many failed studies of treatments in children and young adults, we argue that postnatal neurogenesis and synaptic function are important targets for ongoing studies. A robust research agenda should target overexpressed genes whose products demonstrably impact postnatal neurogenesis, synapse structure and function, or both in mouse and human model systems. It would translate those observations into treatments that specifically target expression of the gene, its products, and the pathways in which they participate through the use of existing reagents and the discovery of novel reagents to support clinical trials. Existing data point to *DYRK1A*, *KCNJ6* (Figure 1b), and possibly *SOD1* as candidates. Potent and specific inhibitors of DYRK1A may enhance the chances for success, and new approaches to KCNJ6 and oxidative stress are encouraged. Data in model systems for aberrant GABAergic neurotransmission argue that therapeutically targeting GABA-mediated signaling may also prove effective. If in DS a role emerges for changes in immune function on cognition, genes encoding interferon receptors may also be suggested (109). Although success targeting glutamatergic and cholinergic neurotransmission is lacking, these topics deserve further investigation. Finally, given the importance of behavioral disorders, it will be important to further explore and validate safety and efficacy of existing treatments for these disorders.

DEFINING TREATMENTS TO PREVENT ALZHEIMER'S DISEASE IN ADULTS WITH DOWN SYNDROME

Alzheimer's Disease in Down Syndrome

Those with DS are at high risk of developing AD, with AD pathology present in virtually all by age 40; the average age at dementia diagnosis is 56, with more than 80% affected by age 69 (8, 110–114). In DS, the extra copy of the gene for amyloid precursor protein (h*APP*) is necessary for AD in DS (AD-DS). h*APP* is highly expressed in central nervous system neurons; the full-length hAPP protein (fl-hAPP) is the precursor of the amyloid-β (Aβ) peptides that accumulate in amyloid plaques. Compelling evidence that increased h*APP* gene dose is essential for AD-DS comes from case reports in which persons partially trisomic for HSA21 (i.e., carrying only two copies of the h*APP* gene) demonstrated neither AD pathology nor dementia, even in old age (115, 116). An increase in wild-type h*APP* copy number has been linked to some familial AD cases (117–119). In spite of many clinical and pathological similarities for AD and AD-DS (9, 14), differences in underlying molecular and cellular mechanisms must be considered. Abundant evidence supports the amyloid hypothesis for AD, under which the Aβ peptide products of *APP* induce pathogenesis (120). Since Aβ species are increased in the DS brain, including in amyloid plaques (121), it is possible that the same pathogenic events occur in AD-DS. However, it is not clear whether Aβ is the only *APP* product involved. Indeed, in AD-DS, increased levels of Aβ are present together with increased levels of other *APP* products. Moreover, AD emerges in the context of other overexpressed HSA21 genes. Accordingly, the amyloid hypothesis of AD is but one means by which to explain the impact of increased *APP* gene dose in AD-DS.

How increased *APP* gene dose causes AD-DS is as yet unclear, but studies of AD pathogenesis point to many possible mechanisms (120, 122, 123) that could be induced. Importantly, studies in model systems in vitro and in vivo converge with those in humans in pointing to an essential role for increased *APP* gene copy number (124, 125). Possible contributions from increased levels of fl-hAPP, its 99-amino-acid C-terminal fragment (β-hCTF), and the Aβ peptide product(s) of β-hCTF have been examined (126–133). A role has been documented for β-hCTF in the activation of the small GTPase Rab5, resulting in enlargement of early endosomes (126, 128–130). Other APP products, including fl-hAPP and Aβ, may also contribute to endosomal enlargement (128), but this is not established (see 127). Dysregulation of the endosomal system may play an incisive role by compromising axonal transport of neurotrophic signals carried in endosomes (126, 128). Indeed, axonal trafficking of signaling endosomes is essential for maintaining neuronal function (for reviews, see 127, 134). Both in vivo and in vitro, endosomes enlarged due to increased Rab5 activity were less effective in transporting neurotrophic signals (124, 128). Neurodegeneration in a mouse model of DS was correlated with *APP* gene dose–mediated reductions in endosomal transport (124). Supporting a link between increased *APP* dose and endosomal dysfunction, a recent report showed that reducing full-length mouse APP (fl-mAPP) and mouse C-terminal fragments (mCTFs) in the Ts65Dn mouse model of DS restored normal levels of Rab5 activity, reduced p-tau, and reversed deficits in activation of the tropomyosin receptor kinase B (TrkB) for brain-derived neurotrophic factor (135). Nixon and colleagues (126) recently expanded on these and earlier findings by showing that forced

increases in the activity of Rab5 caused endosomal enlargement, reduced LTP, reduced AKT signaling, increased p-tau, and caused degeneration of basal forebrain cholinergic neurons. Taken together, the data raise the possibility that AD-relevant phenotypes in AD-DS are linked to endosomal system dysfunction. Studies to fully decipher how *APP* products act to induce pathogenesis are needed.

Preventing and Treating Alzheimer's Disease in Those with Down Syndrome: Current and Future Approaches and Timing

Given that increased *APP* gene dose is necessary for AD-DS, a rational approach to preventing AD-DS would target reducing to normal the levels of *APP* products. *APP* mRNA could be specifically targeted by antisense oligonucleotides or through siRNAs. Small-molecule treatments to reduce translation of the mRNA for fl-hAPP, as was recently reported (135), may prove useful. Cleavage of fl-hAPP by β-secretase (BACE) produces the β-hCTF; subsequent γ-secretase cleavage of β-hCTF yields the Aβ peptide (123). Inhibitors of BACE reduce β-hCTF levels, but recent clinical trials using BACE inhibitors in AD failed due to futility, toxicity, or both; several worsened cognitive decline (136). Given the link between β-CTFs and endosomal dysfunction, it is not surprising that inhibitors of the γ-secretase enzyme failed with respect to outcomes and worsened cognition (137–139). An alternative approach to reducing toxic Aβ peptides employs γ-secretase modulators (GSMs), which enhance processivity of the enzyme, resulting in decreases in Aβ42 and Aβ40 (140). In preclinical studies in PSAPP mice, candidate GSMs reduced plasma and brain levels of Aβ42 and Aβ40 and prevented plaque deposition in young mice (141). Finally, one could target Aβ peptides and toxic oligomers using immunotherapies. In ongoing studies in AD, several monoclonal antibodies are being examined (136), one of which has recently been approved by the US Food and Drug Administration. Given the high incidence of amyloid angiopathy in DS (10), the link between vascular amyloid and amyloid-related imaging abnormalities (ARIAs) (142), and the significant increase in ARIAs in those treated with some monoclonal antibodies to Aβ (143), considerable caution must be exercised with respect to such treatments in those with DS. Ideally, they would be used only after having been proved safe and effective in carefully controlled trials in those with DS at risk of developing AD. Using a different immune-based approach, a recently completed Phase Ib trial tested a vaccine against Aβ in adults with DS; a report of findings is anticipated in the near future, but publicly available data document safety. Data for increased activation of RAB5 and endosomal dysfunction suggest it may be beneficial to reduce RAB5 levels, possibly using antisense oligonucleotides. Finally, in the context of endosomal dysfunction, DYRK1A emerges as a possible target. Indeed, among its substrates are fl-APP and presenilin. Presenilin is a component of the γ-secretase complex that cleaves the CTFs of fl-hAPP; by cleaving the β-hCTF, this complex produces Aβ. In addition, DYRK1A targets numerous proteins involved in regulating endocytosis (56) (Figure 1c).

Studies of other possible treatments for AD-DS have been reported. ELND005, or scyllo-inositol, has antiaggregation effects on amyloid, a finding that prompted a Phase II, 4-week, randomized, double-blind, placebo-controlled study in 23 adults with DS, ages 18–45, without dementia. Treatment was safe, but small numbers and short treatment duration may have contributed to the absence of effects on cognitive or behavioral

measures (144). Addressing cholinergic neuron loss and positive effects in AD, trials of the cholinesterase inhibitors donepezil, rivastigmine, and galantamine were carried out in adults with DS. Work evaluated in the *Cochrane Database of Systematic Reviews* included only randomized, placebo-controlled trials. Donepezil was tested in one small ($n = 30$), 24-week study in AD-DS. Adverse events, which included diarrhea, insomnia, nausea, and fatigue, were more frequent in the donepezil group. Although some benefit was suggested, no significant differences in cognitive or behavioral outcomes were demonstrated (145). No rivastigmine or galantamine trials met the criteria for evaluation (146, 147). Hanney and colleagues (148) examined another drug used to treat AD by evaluating the effects of memantine in a randomized, double-blind, placebo-controlled, 52-week study in 173 adults with DS older than age 40. There was no benefit in cognitive or functional outcomes. Thus, the successful use of cholinesterase inhibitors and memantine in AD was not replicated in AD-DS. Observations on the loss of locus coeruleus neurons in the Ts65Dn mouse encouraged studies on restoring norepinephrine levels and signaling using L-threo-3,4-dihydroxyphenylserine (L-DOPS)/carbidopa and β-adrenergic agonists, both of which reversed contextual learning deficits (125); as far as we are aware, no clinical trials examining the efficacy of these compounds in elderly adults with DS have been undertaken. Focusing on oxidative stress, a 2-year, randomized, double-blind, placebo-controlled study in 53 people with AD-DS tested daily oral treatments combining α-tocopherol, ascorbic acid, and α-lipoic acid. Treatment was safe, but there was neither improvement in cognition nor a reduced rate of decline (149). A trial that enrolled adults with DS older than 50 found that treatment with α-tocopherol for 3 years failed to slow progression of cognitive decline (150).

Ideally, treatment for AD-DS would be initiated before the onset of a disorder (i.e., to effect primary prevention). The emergence of highly informative clinical biomarkers may enable early intervention (151–153). Remarkably, recent biomarker findings suggest that disease progression is correlated with age (154), thus enabling trials to recruit on the basis of age to enroll disease stage–matched cohorts. Clinical trials require accurate, sensitive measures of cognition. Recent progress is encouraging (155), but it will be essential to employ validated measures. Although challenges for conducting trials in AD-DS should not be underestimated, the creation of new measures and assembly of trial-ready cohorts is encouraging. The use of novel trial designs and emphasis on treatments with favorable long-term toxicity profiles may prove helpful.

SUMMARY AND CONCLUSIONS: A WAY FORWARD FOR DOWN SYNDROME TREATMENTS

Although no treatments specifically targeting DS have been approved, our review notes several advances that promise future DS therapeutics. Increasing knowledge of the DS genetic landscape, improved rodent and human model systems, and the development of treatments for specifically targeting genes and mechanisms promise enhanced discovery of treatments. Understanding that increased expression of specific HSA21 genes is necessary for DS phenotypes supports a rationale under which work in model systems targets genes whose overexpression is shown to contribute necessarily to phenotypes. A caveat is that

normalizing expression of such genes may prove ineffective if downstream pathogenetic events have been irreversibly induced. This caveat may be gene specific but has not yet been adequately tested. It follows that one should treat as early as possible. Current use of existing symptomatic treatments should be tested to demonstrate safety and efficacy in DS.

To support new treatments, we recommend (*a*) developing measures of brain growth during the fetal period; (*b*) developing DS-specific measures of cognition and behavior across the life span; (*c*) discovering biomarkers of brain function in DS; (*d*) building cohorts for natural history studies in both young and old people with DS; (*e*) establishing centers of clinical and research excellence for DS; (*f*) increasing the number and utility of model systems, including nonhuman primates; and (*g*) engaging academics and industry in discovering treatments and designing clinical trials. These next steps may usher in a new era of treatments for DS.

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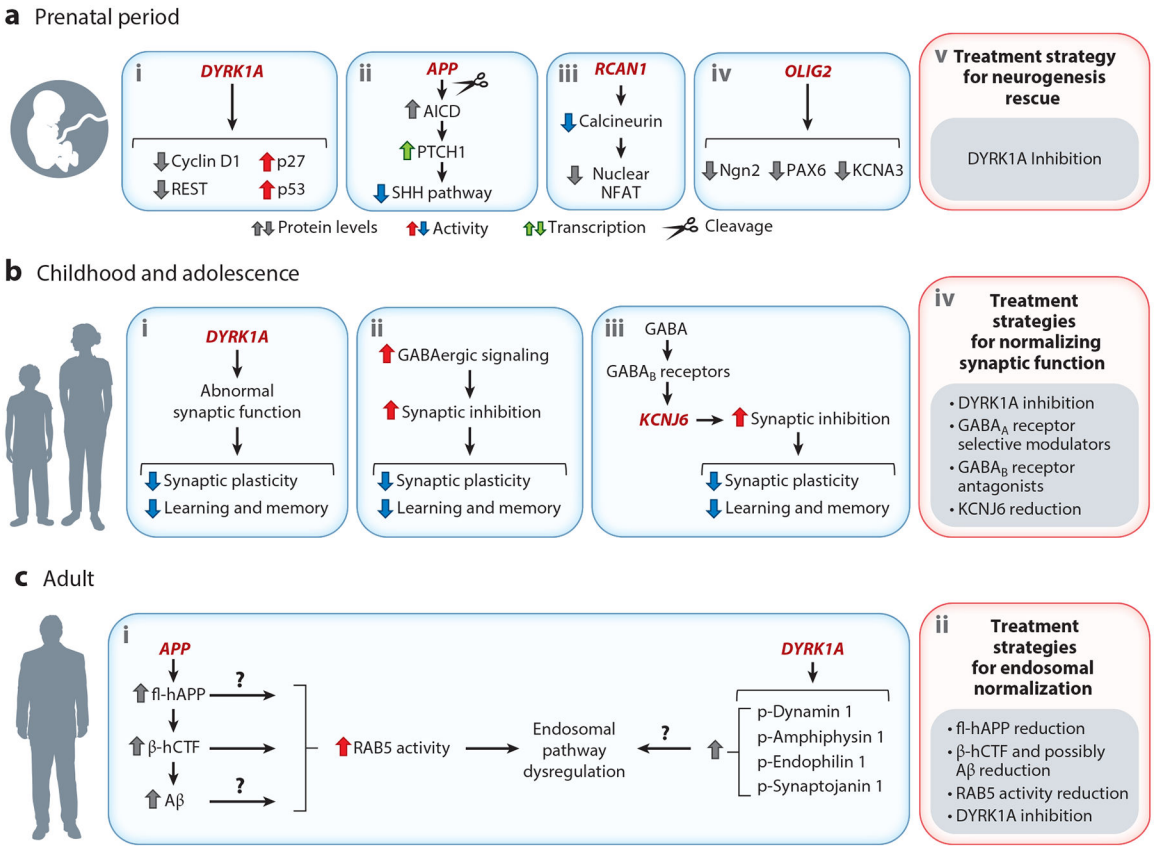

Figure 1.

(*a*) Key triplicated genes involved in early neurogenesis impairment in DS and possible prospects for treatment. (*i*) *DYRK1A* overexpression. Overexpression of *DYRK1A* reduces levels of cyclin D1, a protein that promotes G_1- to S-phase transition; increases the activity of p27 and p53, two key regulators of cell cycle progression; and reduces the levels of REST, a key regulator of pluripotency and neuronal differentiation. All these effects cause cell cycle disruption and premature exit from the cell cycle. (*ii*) *APP* overexpression. Cleavage of APP gives rise to various derivatives, including AICD. Excessive AICD levels increase the transcription of the mRNA for *PTCH1*, an SHH receptor that keeps the mitogenic SHH pathway repressed, thereby hampering proliferation. (*iii*) *RCAN1* overexpression. RCAN1 inhibits the activity of calcineurin, a protein phosphatase that activates the transcription factor NFAT by dephosphorylating it. Excessive inhibition of calcineurin due to *RCAN1* overexpression maintains NFAT in the phosphorylated state, thereby preventing its translocation to the nucleus and its proneurogenic effects. (*iv*) *OLIG2* overexpression. Enhanced expression of the transcription factor *OLIG2* causes downregulation of neuronal specification factors, including Ngn2 and PAX6, and inhibits the expression of KCNA3, a K^+ channel that influences cell growth and differentiation of neural progenitors. Available evidence points to increased gene dose for *DYRK1A* and *APP* as particularly critical determinants of neurogenesis failure in DS. The roles for increased gene dose for *RCAN1* and *OLIG2* have been less extensively investigated so far (see 16 and 54 for more detail). (*v*) Prospects for treatment. Evidence in DS models shows that treatments targeting the *DYRK1A*- and *APP*-dependent pathways can fully restore

neurogenesis. Treatments targeting *APP* and *APP*-dependent pathways are attractive, but at this time, *DYRK1A* represents the gene candidate of choice with inhibition of DYRK1A as an attractive possibility. (*b*) Key triplicated genes and pathways involved in reduced synaptic plasticity and learning in DS and prospects for treatments. (*i*) *DYRK1A* overexpression. Increased expression of *DYRK1A* in mouse models of DS results in reduced synaptic plasticity and defects in learning and memory. (*ii*) GABAergic signaling. Increases in GABAergic signaling through both $GABA_A$ and $GABA_B$ receptors are linked to reduced synaptic plasticity and learning in mouse models of DS. (*iii*) *KCNJ6* overexpression. GABA signaling through $GABA_B$ receptors is mediated by inwardly rectifying K^+ channels, one subunit of which is encoded by *KCNJ6*. The resulting increase in inhibition is responsible for reduced synaptic plasticity and deficits in learning and memory in a mouse model of DS. (*iv*) Prospects for treatments. Several approaches are recommended. Inhibition of DYRK1A, antagonists and/or modulators of $GABA_A$ receptors and antagonists of $GABA_B$ receptors, and reduced expression of *KCNJ6* could be considered. (*c*) Key triplicated genes and pathways possibly involved in endosomal dysregulation in AD in DS and prospects for treatments. (*i*) *APP* and *DYRK1A* overexpression. The β-hCTF product of fl-hAPP induces activation of RAB5 (i.e., increases the levels of RAB5-GTP) and, via this mechanism, results in dysregulation of the endosomal pathway, leading to reduced transport of neurotrophic signaling and likely a host of other changes deleterious to neuronal function. Whether fl-hAPP, the Aβ peptide product of fl-hAPP, or both also activate RAB5 is an active area for research. DYRK1A acts on several proteins that regulate endocytosis; increased DYRK1A activity may further exacerbate changes in endosomal function. (*ii*) Prospects for treatments. Several approaches are rational. In one, treatments that decrease the levels of fl-hAPP and its products can be explored. Alternatively, one could attempt to reduce the levels or activity of the β-hCTF. Whether endosomal function is normalized by reducing the levels of Aβ peptides through modulation of γ-secretase or through immune approaches has yet to be demonstrated. Another approach would target reducing the levels of RAB5-GTP, possibly by reducing its mRNA levels. Finally, the effects of DYRK1A inhibition could be explored. In all panels, italics signify a gene; names in roman type refer to the protein or mRNA. Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; AICD, APP intracellular domain; APP, amyloid precursor protein; β-hCTF, β-C-terminal fragment of fl-hAPP; DS, Down syndrome; DYRK1A, dual specificity tyrosine-phosphorylation-regulated kinase 1A; fl-hAPP, full-length human APP; GABA, γ-aminobutyric acid; KCNA3, potassium voltage-gated channel; KCNJ6, G protein–activated inwardly rectifying potassium channel; NFAT, nuclear factor of activated T cells; Ngn2, neurogenin 2; OLIG2, oligodendrocyte transcription factor 2; p27, cyclin-dependent kinase inhibitor 1B; p53, phosphoprotein p53; PAX6, paired box 6; PTCH1, patched 1; RAB5, Ras-related protein RAB-5; RAB5-GTP, guanosine triphosphate–bound (i.e., activated form of) RAB5; RCAN1, regulator of calcineurin 1; REST, neuron-restrictive silencing factor; SHH, Sonic hedgehog.

Table 1

Cognitive functions in children and young adults with DS

Cognitive functions		Profile
IQ		IQs average 50 and range from 30 to 70 (61)
Memory	Verbal short-term memory	Impairment relative to MA-matched TD groups and other ID groups (62)
	Nonverbal short-term memory	In comparison to MA-matched TD groups, comparable or poorer performance In comparison to other ID groups, comparable or stronger performance (62)
	Verbal long-term memory	Impairment relative to MA-matched TD groups and other ID groups (63)
	Nonverbal long-term memory	Impairment in visual associative memory, visual recognition, and spatial memory compared with MA-matched children Similar or stronger visual memory than groups with mixed ID or WS (64,65)
	Implicit memory	Comparable to MA-matched TD groups (66)
Language	Expressive and receptive language	Expressive language more affected than receptive language (67)
	Lexicon	Lower performance on both comprehension and production tasks compared to MA-matched TD children (67)
	Morphosyntactic skills	Particular impairment in expression and comprehension (67)
Visuospatial perception	Visuospatial construction	Performance on block design task consistent with cognitive level; similar performance to other ID groups; stronger performance than WS; mixed findings on figure-copying tasks (68)
	Mental rotation	Less accurate than MA-matched TD groups (68)
	Closure	Impairments relative to MA-matched TD groups Poorer than other ID groups (e.g., FXS) (68)
	Wayfinding	Particularly poor in comparison to TD individuals and other ID groups (68)
Executive functions	Attention	Impairment in auditory sustained attention and visual selective attention (69)
	Planning	Comparable accuracy but longer execution times than MA-matched groups (69)
	Shifting	Lower performance than TD individuals and other ID groups on verbal shifting (69)
	Inhibition	Impairment in the verbal modality Less severe visual inhibition deficit (69)
	Working memory	Significant impairment relative to TD individuals; mixed findings in comparison to other ID populations (69)

Abbreviations: DS, Down syndrome; FXS, fragile X syndrome; ID, intellectual disability; IQ, intelligence quotient; MA, mental age; TD, typically developing; WS, Williams syndrome.

Table 2

Psychiatric comorbidity in children and young adults with DS

Psychiatric comorbidity	Symptoms
Prevalence	Increased prevalence of behavioral and mental health problems compared with the general population Lower risk of psychopathology compared with children with other IDs (70)
Developmental trajectories	High rates of hyperactivity, impulsivity, tantrums, and agitation In adolescence, decline of externalizing behaviors and higher rates of internalizing behaviors such as social withdrawal, depression, and anxiety (70)
Associated features	Mixed results on the relationship between the degree of ID and problem behavior (71)

Abbreviations: DS, Down syndrome; ID, intellectual disability.