Cognitive, Psychological and Social Functioning Associated with SDS

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Overview

SDS and the Brain

Neuropsychological Challenges in SDS



Shwachman Diamond Syndrome (SDS)

- Rare genetic disorder (1/76,000 live births)
 - caused by mutations in the *Shwachman-Bodian-Diamond-Syndrome (SBDS)* gene, at chromosome 7q11 (Boocock et al., 2003)
- Approximately 90% of individuals who meet clinical dx of SDS have mutations in the *SBDS* gene
 - mutations in the *DNAJC21*, *EFL1*, and *SRP54* genes have also been associated to a SDS phenotype
- *SBDS* protein plays a role in ribosome biogenesis
- *SBDS* is expressed in all organs including the brain



Cryo-EM map showing the large ribosomal subunit (cyan), eIF6 (yellow) and **the SBDS protein** (magenta) that is deficient in Shwachman-Diamond syndrome.

Credit: Alan Warren, University of Cambridge

Brain 101: The Power of the Neuron



A single neuron in the brain. We have about 86 billion neurons in our brain

Anatomy of a Neuron



Brains work by sending messages from one part to another

- The neurons communicate with each other through electrical impulses triggered by the activity of neurotransmitters.
- The system is interconnected.
- Compared to the complex electrical system of a big city







Human Brain: Altered structures & Connectivity

Gray Matter

White Matter

SDS - right hemisphere Controls- right hemisphere



Connectivity



Transformed thickness	Delayed myelination, reduced volume, diffusion abnormalities, agenesis of the corpus colosseum, intensity changes on posterior pons and globus pallidus	Alterations in the fronto-occipital fasciculus, inferior-longitudinal fasciculus;, arcuate fasciculus, limbic, anterior cingulate, and ponto-cerebellar fasciculus; anterior cingulated and arcuate fasciculus
Toivianinen-Salo et al. 2008 Booij et al. 2013 Perobelli et al. 2015	Kamoda et al. 2005, Todorovic-Guild et al. 2006; Toivianinen-Salo et al. 2008; Booij et al. 2013; Perobelli et al. 2015; Bans et al. 2018	Perobelli et al. 2015 Elizabeth N. Kerr, PhD, CPsych. SDS talk November 22, 2020

Neurodevelopment Disorders:

- Impairments of the growth and development of the brain and/or central nervous system either prenatally or early postnatally
- Genetic predisposition/ genetic abnormalities & external environmental influences
- Dysregulated ribosomal biogenesis is a target in the pathogenesis of some neurodevelopmental disorders (Hetman and Slomnicki 2018; Slomnicki et al. 2016)



Neurodevelopmental Studies





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THE JOURNAL OF PEDIATRICS • www.jpeds.com



The Behavioral Phenotype of School-Age Children with Shwachman Diamond Syndrome Indicates Neurocognitive Dysfunction with Loss of Shwachman-Bodian-Diamond Syndrome Gene Function

Elizabeth N. Kerr, PhD, Lynda Ellis, RN, Annie Dupuis, PhD, Johanna M. Rommens, PhD, and Peter R. Durie, MD, FRPC (C)

N= 32 children ages 6 to 17 with SDS

Results compared to:

(1) Normative Data

(2) 13 siblings without SDS

- (3) 21 age and gender match children with Cystic Fibrosis
 - leading cause of childhood pancreatic insufficiency

Parent Report of Early Development

Delays in early developed are reported; Kent et al. 1990; Cipolli et al. 1999; Kerr et. al. 2010

Delays in Motor Milestones Delays in Language Milestones • 55 % late to crawl • 50% late to speak one word • 39% late to walk • 53% late to speak in sentences Kerr et al. 2010 Kerr et al. 2010 N= 32 N=32 Obtain OT, PT and Speech and Language Therapy as indicated

Parental Report of Learning Issues



- 68% from Italian registry reported issues
 - 9% serious, 40% with support
 - Perobelli et al,. 2011
 - 70% of those on the French registry report difficulties
 - Doandieu, SDS Congress Verona 2016
- 95% from US registry report significant concerns:
 - learning
 - emotional (mood, depression)
 - social issues
- Loveless et al. 2018

Neuropsychological Assessment

in order to understand brain-behaviour relations



Role:

Assessment of cognitive, psychosocial, and adaptive functioning Analyze and interpret findings based a number of factors Diagnostic and prognostic Inform optimal treatment Monitor development and response to treatment

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Understanding Assessment Results



Intellectual Abilities

Numerous studies report weaknesses Aggett et al. 1980, Kent el al . 1990, Cipolli et al. 1999, Kerr et al. 2010, Perbobelli et al. 2015

A range of abilities is observed (Kerr et al. 2010):

Overall IQ: 6% performed above Average & half performed below Average

• Significantly lower than normative data as well as siblings and CF controls (p>.001 for all)

Visual & Verbal IQ: Half performed below Average [X = 86.6 (17.6) & 93.5 (18.3)]

- Significantly lower than norms (p <.001 and p=.05 respectively)
 - $\circ~$ Visual IQ & Social Comprehension were significantly lower than norms, siblings, & CF controls



1 in 5 meet DSM-IV criteria for an Intellectual Disability

Strategies to Support Weak Reasoning

General Strategies for School/Home

- Check for understanding
- Provide concrete examples
- Teach reasoning overtly by talking out loud, modelling, and offering rehearsal
- Be direct express complex ideas as simply as possible
- Provide opportunities for experiential learning

At Home

- Play games
- Problem solve out loud
- Support classification skills

Processing Speed:



Visual-Motor Processing Speed

Significantly weaker than norms, siblings and CF controls

IMPLICATIONS:

- Slower motor output
- Slower reaction times
- Difficulty working methodically
- Difficulty keeping pace
- ➢ Gaps in learning & frustration

STRATEGIES:

- Speak at a slower pace & provide concise information.
- Offer longer times for writing tests & exam s
- Avoid competitions (fastest first, bell ringer tests)
- Simplify tasks by dividing information into chunks.
- Use cueing mechanisms to prepare student for changes.
- Teach independent strategies (e.g. write lists, pack homework and class notes into knapsack after each subject to avoid rushing at the end of the day).
- Provide visual/written information to support verbal instructions.
- Provide a note taker or permit use of an audio or video recorder for lessons.
- Provide learning resource support to recap and fill in gaps in learning.



Visual-Motor Integration



Significantly weaker than norms, siblings and CF controls

STRATEGIES: Fine Motor Issues

- Ensure s/he has a note taker
- Request handouts of all board work
- Request opportunity to take test orally
- Request extra time for assignments and test
- Consider cursive writing rather than printing
- Consider key-boarding instead of cursive

Higher Order Language Kerr et al. 2010



Making Inferences Significantly weaker than norms



Understanding Figurative Expressions Significantly weaker than norms, siblings & CF controls



Knowledge of Synonyms Significantly weaker than norms, siblings & CF controls

STRATEGIES

- Use pictures: "what's going on in the Picture?"
- Use wordless books (e.g., by David Wiesner)
- Watch Pixar short files (e.g., "For the Birds", "The Blue Umbrella", "La Luna", Presto")
- Explicitly teach analogies, similes, etc
- Problem solve together (i -locate figurative language in text; ii -decipher the literal meaning and determine if that is the message the author is trying to convey; & iii - use background knowledge abut the word or phrase to decide what was actually intended.
- Connect to the real world/life
- Use visual imagery (e.g., "cut it out")
- Explicitly teach synonyms and antonyms
- Encourage the use of thesaurus to explore words

Executive Functioning



figure out how to accomplish our goals.

Planning is the ability to

Time Management is

having an accurate understanding of how long tasks will take and using time wisely and effectively to accomplish tasks.



Working Memory is the mental processes that allow us to hold information in our minds while working with it.

STOP

Self-Control is the ability to regulate yourself, including your thoughts, actions, and emotions.

> **Perseverance** is the ability to stick with a task and not give up, even when it becomes challenging.



Organization is the ability to develop and maintain a system that keeps materials and plans orderly.

Task Initiation is the

ability to independently start tasks when needed. It is the process that allows you to just begin something even when you don't really want to.





Metacognition is being aware of what you know and using that information to help you learn.

Attention is being able to focus on a person or task for a period of time and shifting that attention when needed.



Flexibility is the ability to adapt to new situations and deal with change.

Attention	Kerr et al N=32 (6 to 17 years)		Perobelli et al N=33 (3 to 17 years)		Loveless N=49 (<1-69)
Parent-Proxy Report	SDS	CF	SDS	CF	SDS
Inattention	50% *	28.6%	29%*	0	50%

* Significantly higher than norms and controls subjects with CF

Formal Assessment

- Span
- Working memory
- Selective
- Sustained

80% performed below the Average



Sustained Attention

SDS group performance across attention tasks was significantly weaker than Norms

SDS performed significantly weaker than CF controls in all but selective attention

Strategies to Support Attention

- Inattention and ADHD are significantly more common in children with SDS than in the general population
- Educational and behavioural supports used for any child with attention problems can be effective for children with SDS

At School and at Home:

- Set up the environment to reduce distractibility.
- Gain attention before giving instructions: use eye contact/child's name.
- Provide clear, explicit, concise instructions.
- Tailor appropriately paced/time activities.
- Use visual prompts: timetable or checklists.
- Use engaging and varied activities, emphasizing the child's interests.
- Provide prompts to attend (look, listen, respond).
- Modify/limit the task length (clear beginning/clear end).
- Have child identify something to look forward to after the work is done.
- Provide regular work breaks.
- Identify and encourage strengths.
- Assist in breaking down information into short pieces that are "do-able".
- Offer a lot of positive feedback and try to limit corrective feedback.

Executive Functioning: High incidence of impairment



* significantly lower than norms, siblings and CF control

Deficits seen in SDS patients relative to their intellectual functioning

Strategies: Executive Functioning

- Set up routines for the child to follow
 - When activities become habitual, they require less active processing and are less likely to be forgotten
- Use short instructions and provide a checklist of steps to complete
- Use eye contact
- Modify the task to support development
- Provide regular breaks, including those with physical experience
- Limit multi-tasking
- Model problem-solving explicitly (thinking aloud)

Play Modifies Development of the Prefrontal Cortex

- Educational games induce more knowledge and skills acquisition than conventional instruction (Wouters et al 2013)
- Cognitively demanding games improve cognitive (see Fissler et al. for Review)

Components

- Challenge and adapt
- Intensive time matters!
- Motivate and engage
- Cross-train





"70 Play Activities for Better Thinking, Self-Regulation, Learning & Behavior" by Lynne Kenney Enhancing and Practicing Executive Function Skills with Children from Infancy to Adolescence



Center on the Developing Child 🕎 HARVARD UNIVERSITY

http://developingchild.harvard.edu/wp-content/uploads/2015/05/Enhancingand-Practicing-Executive-Function-Skills-with-Children-from-Infancy-to-Adolescence-1.pdf Elizabeth N. Kerr, PhD, CPsych. SDS talk November 22, 2020

Memory Is Solid Overall

Kerr N=32 2010

Visual Memory

- Immediate recognition for faces NS
- Delayed recognition for faces NS

Auditory Memory

- List learning and retention NS
- Immediate recall for stories NS
- Delayed recall for stories -p=.01

Perobelli N= 9 2012

- Reported that incidences of verbal and non-verbal memory were significantly weaker than controls
- However, median centiles were within Average range and Controls were above Average

Psychological Well-Being

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		Kerr et al N=32 (6 to 17 years)		Perobelli et al N=33 (3 to 17 years)	
	Parent-Proxy Report	SDS	CF	SDS	CF
	Somatic complaints	40.6%*	19%	24%*	12%
	Rule-breaking behaviour	28.6%*	14.3 %	Highe Norm	er than s &CF
	Anxiety/Depression	20%*		Some diffic	e with ulties

• Significantly higher than norms and controls subjects with CF

Psychological Well-being Parent-Proxy Report

	Kerr et al. 2010 N=31
Restless/ Implusive	43.8%
Hyperactive	31.3%
Acting/Shy	40.5%
Oppositional	31.3%
Aggressive	31.2%
Emotional Lability	28.1%

• Self-identified concerns about prognosis (risk of leukemia or need for transplant) and transition to adulthood (Loveless et al. 2018)

Strategies to Support Behaviour

- Make expectations clear
- Have a predictable daily schedule
- Explicitly teach routines
- Give clear directions
- Use language that promotes self-regulation (e.g., it is "time to calm down", "Try to think of something else", "count to ten and breathe out" etc.)
- Help de-escalate problems by using distractions appropriate for the student (e.g., humour, change of scene/activity/person working with him or her
- Present options when a child has trouble with frustration (What would help you to get this done: working with me or having a quick break and working on you own?"
- Build movement into the day and activities to help with mental stamina, and better behaviour.
- Make consequences immediate
- Ensure your child understand why his or her behaviour was a problem
 - Incorporate "Social Mapping" to support understanding of the outcomes of expected behaviours and unexpected behaviours.

Resource: https://childmind.org/guide/parents-guide-to-problem-behavior/

Strategies to Support Well-Being

- Celebrate strengths
- Support growth mindset
- Normalization
- Inclusivity



Support from a counsellor, SW, psychologist

Social Functioning



Kerr et al N=32
6 to 17 years of agePerobelli et al N=33
3 to 17 years of ageSDSCF

Parent-Proxy Report Social Problems

Significantly higher than norms and controls subjects with CF

9.5%

Formal Assessment

Kerr et al. 2010

- Social Comprehension = 58%
- Higher Order Language
 - Figurative Language= 46%

34%

Inferences = 56%

Blatt et al. 2017 n=7

Social Cognition

Parent Report

Kerr et al. 2010 6 % prior DX of ASD

Loveless et al. 2012

- n = 49 (<1 -67 years of age)
- High rates of social anxiety

31%

- Social difficulties due to short stature and often missing school
- Delayed maturity relative to peers

6%

Adaptive Functioning Kerr et al. 2010

AF refers to social-cultural standards for personal independence

- Covers a wide range of developmentally driven functional competences
- Broad functional independence and Community living skills of the SDS participants were significantly lower than norms, Siblings and CF controls (p=.0188, p=.0005, p=.0023 compared to norms and p=.001, p=.0017, p=.0017 compared to CF; Kerr et. al. 2010
 - Even those with typical intellectual abilities display limitations in AF
- Medical issues may necessitate dependence on family at a time when independence is key
- > Parents may be vigilant & be reluctant to facilitate total independence

AF is an indicator of positive life outcomes (educational, interpersonal, & employment)

Generic patient-reported outcomes in child health research: a review of conceptual content using World Health Organization definitions

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Concept to measure	Definition used	Graphic representation	Item example
Functioning, disability, and health (FDH)	The interaction or the individual components of body functions, activities and participation that occur in the context of the environment or personal factors	Health Condition Body functions Environment Body Health Condition Participation Personal factors	In the past 4 weeks, how difficult has it been to walk short distances? (not at all to extremely difficult)
Health-related quality of life HRQOL (a sub- component of quality of life) ^a	A child's goals expectations, standards or concerns <i>about</i> their overall health and health-related domains	choices expectations Functioning, disability, and health concerns 1 goals/priorities standards	In the past 4 weeks, how satisfied have you been with your ability to walk short distance? (very dissatisfied to extremely satisfied)
Quality of life QOL	A child's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.	choices health resources concerns	My life is as good as I ever expected (strongly agree to strongly disagree)

FDH and Quality of Life



- Child Health Questionnaire (N= 7 child/parent diads): ages 5-18 (Silwal, Kinsey, & Puntis 2014)
 - ~60% of the items relate to functional disability and health
 - ~ 33 % of questions relate to QofL
- More than 50% of parents reported Below Average scores:
 - Child's general health
 - Worry due to child's physical and /or psychosocial health
 - Uncertainty about their child having a healthly life
 - Difficulty with school work and/ or socially
 - Child's health interrupted family activities or was the source of family tension

Further Characterization of Shwachman—Diamond Syndrome: Psychological Functioning and Quality of Life in Adult and Young Patients

Sandra Perobelli,¹* Elena Nicolis,² Baroukh Maurice Assael,¹ and Marco Cipolli¹ ¹Cystic Fibrosis Center, Azienda Ospedaliera Universitaria Integrata, Verona, Italy ²Laboratorio Analisi Chimico Cliniche, Azienda Ospedaliera Universitaria Integrata, Verona, Italy

Survey & SF-36 patients included in the Italian SDS Registry- 86% response rate

- SDS adults =17; 3-17 year olds = 33
- Patients with SDS scored lower than those with CF in physical performance (walking, running, climbing stairs, lifting weights) and physical pain, limiting daily living activities. FDH
- Adults show lower incidence of independent living/housing, marriage, employment and driver's licence obtainment relative to CF controls. FDH

HRQOL Adults

 Lower satisfaction of socialization than CF

	SDS	CF	P-value
'Focussing on the last	Mean (sd)	Mean (sd)	
12 months,			
what is your degree			
of satisfaction			
about" (score 1–4,			
"very low"—"very high")			
Relations within family	2.9(0.8)	3.4(0.5)	0.03
Relations with friends	2.6(0.9)	3.4(0.6)	0.01
Leisure time	2.8(0.7)	3.1(0.7)	0.009
Main occupation	2.2(0.8)	3(0.8)	
(study/work)			
Personal finance	2.2[1.1]	2.8(0.6)	
Does your current	n. ("yes")	n. ("yes")	
health status			
cause any problem			
on" [Yes/No]		•	
Job	4	3	0.0002
House maintenance	3	2	
Social life	6	3	
Family life	2	0	
Sexual life	4	1	
Hobbles	6	1	
Vacation	21(26)	12(0)	
of "upp" provide	51(20)	12(2)	
or ges answers			

Strategies to Support Autonomy and Prosocial skills

- Provide opportunities that will help the student develop a sense of mastery
- Support the development of decision-making skills and resiliency.
- Encourage and support self-management and advocacy
- Model and explicitly teach appropriate social behaviour
- Teach alternative behaviours to achievement the student's social goal (e.g., other ways to gain attention, other ways to create fun)
- Model ways of showing interest and respecting personal space
- Incorporate "Social Mapping" to support the student's understanding of what is acceptable and how to meet the expectations

Neurodevelopmental Issues and SDS



POGO Pediatric Oncology Group of Ontario

- Guide for educators and counsellors
- Potential challenges and implications for school and work
 - Motor
 - Physical excretion
 - Medical
 - Attention & working memory
 - Processing speed
 - Memory & learning
 - Executive functioning
 - Language
 - Autonomy
 - Identity
 - Mental Health & Behaviour

Pathways to Success

FOR YOUTH FACING NEUROCOGNITIVE CHALLENGES

A guide for educators and counsellors



https://www.pogo.ca/wp-content/uploads/2014/10/SAVTI-WEB-BOOKLET-Eng.pdf Elizabeth N. Kerr, PhD, CPsych. SDS talk November 22, 2020

Fatigue: recommendations for teachers

- Offer less intensive classes later in the day.
- Reduce the amount of work you expect the student to complete within a specific amount of time.
- Offer frequent breaks.
- Do assessments over a series of several days.
- Reduce the amount of homework you assign.
- Develop a communication plan with the parent and student to document seizure activity, medication changes and side effects.
- Reduce the course load for older students.



Neuropsychological Monitoring

- 1. Indicators of brain involvement
 - Neuropsychological difficulties in individuals with SDS appear to be primary consequences of SBDS gene dysfunction on the brain
- 2. Risks for mental health and psychosocial functioning
 - Concerns about prognosis
 - Effects of the visible characteristics of SDS on social interaction, behaviour, or self-esteem in individual patients
 - Doctor's app'ts/hospitalization may interfere with inclusion in activities
 - Coping with treatments
- 3. Evaluate Response to Treatment
 - Some are known to affect cognition, mood, and/or behaviour
 - Anabolic steroids
 - Immunosuppressive medicine
 - HSCT
 - BMT in young children
- *4.* Our brain continue to develop based on the continual stimulation from the environment.

Cognitive/Social Stress Points

- Kindergarten > Social Interaction & Learning to <u>learn</u>
- Grade 1 > Learning to <u>read</u>

- High School → Learning to organize on <u>one's own</u>
- College/University ≻ <u>Doing</u> it on one's own



Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome

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	Age	At Diagnosis	Follow-up
Standardized Developmental Screening	Infancy/Preschool	Yes	As indicated
Neuropsychological Assessment including cognitive functioning, psychosocial well-being, AF, & QofL	6-8 11-13 15-17	If late DX	Yes

Concluding Remarks



- The cognitive, psychological, and social consequences of SDS are secondary to structural changes in the brain presumed to be due to dysfunction of the ribosome.
- The neurodevelopmental issues in SDS are lifelong.
- Early identification and intervention will lead to improved outcomes for effected children and their families.