Targeted therapies for behavioral disorders among children with congenital CMV infection

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Université de Montréal

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CONFLICTS OF INTERESTS & DISCLOSURES

- Disclosure: I am pediatric infectious diseases specialist, not a developmental pediatrician!

- COI: In-kind support for CMV testing Altona Diagnostics

LEARNING OBJECTIVES

1. To review how cCMV infection can manifest at sensory integration disorders with dysregulated behaviour in childhood

2. To describe commonly diagnosed behavioural disorders among children with cCMV infection

3. To describe the combined use of both stimulant and non-stimulant medications and no-pharmacological approaches for maladaptive behaviours among children with cCMV

THE NEED FOR MULTIDISCIPLINARY CARE

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- Prior to 2018, Congenital CMV (cCMV) infection managed:
  - Pediatric Infectious diseases clinic, general pediatrics, family medicine.
  - No systematic approach to longitudinal follow-up
  - Counted on everyone ”Following the guidelines”
- Since 1997: Multidisciplinary care center for HIV infection (HIV exposed and Infected kids)
  - Followed infectious diseases guidelines & beyond
  - Structured longitudinal follow-up
  - Neurodevelopmental assessments and interventions
  - Integrated clinical care and research

2018: CENTRE D'INFECTIOLOGIE MÈRE ENFANT

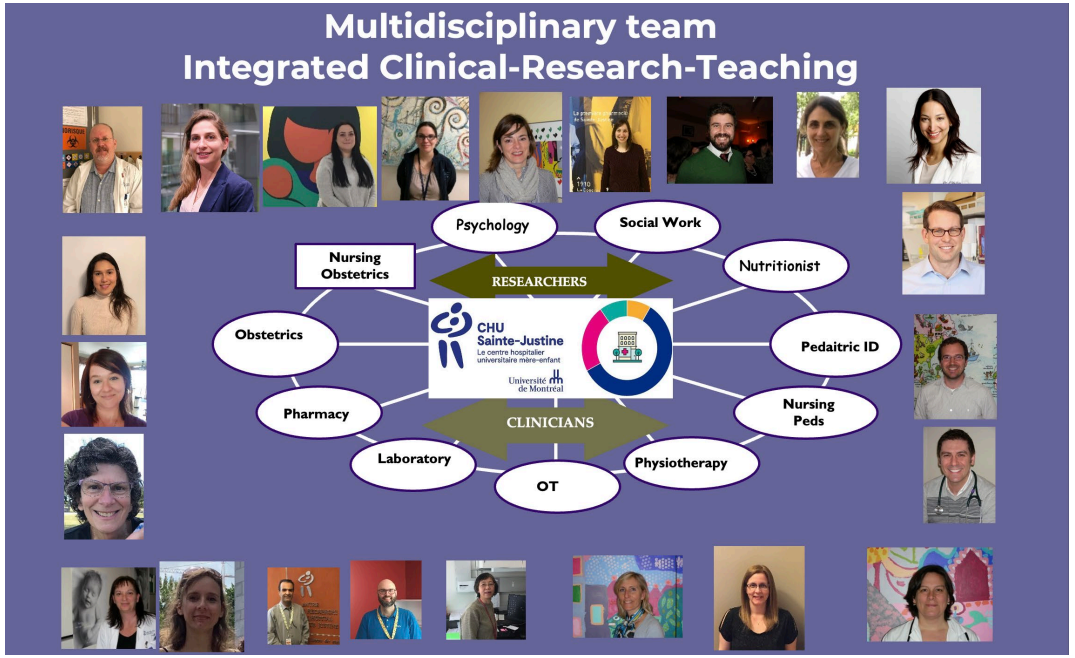
Montreal

Sainte-Justine Hospital opens new centre aimed at combating congenital infections

Women and Children's Infectious Diseases Centre brings hospital's experts into single, multidisciplinary team

Isaac Olson · CBC News · Posted: Sep 26, 2018 5:26 AM EDT | Last Updated: September 26, 2018

The Mother and Child Infectious Diseases Centre at Sainte-Justine Hospital will bring together all the hospitals' experts to offer expectant and new mothers and their babies multidisciplinary care. (Radio-Canada)



CIME

Centre d'infectiologie mère-enfant

CCMV FOLLOW=UP

- 118 children followed to date (20-30 new cases annually)
- Intensive follow-up first 6 months (monthly blood work, audiology, as need physiotherapy, occupational therapy, nutrition, social work, pharmacy) = Wed clinics
- 12 & 18 months, annual follow-up ages 2-5, offered bi-annual thereafter
  - Thursday well-child clinics (coordinated with audiology)
  - Pediatric infectious diseases doctors (trained pediatricians) (first-line assessment)
  - Referral to developmental Peds if concerns (second-line)

“THURSDAY AFTERNOON ISSUES”

WELL-CHILD CLINICS

EXAMPLE: BABY GIRL S.

- Baby girl born at 37 weeks GA, tested for CMV due to
  - Symmetric IUGR , Failed hearing test (unilateral), Microcephaly
    - Head US: Thalamic cysts and LSV, MRI: Diffuse white matter changes biparietal, bi-frontal
- Treated with oral valganciclovir x 6 months
- Tolerated treatment well no complications, “Fussy colicky baby”

Review:

- Meeting developmental milestones (motor, cognitive) slight language delay
- “Clumsy” bumps into things a lot but active, loves trampoline, jumping, always moving
- “Well-child” attends daycare, intelligent, curious

AGE 4

- Annual visit, **all is well** but there's this one thing doc…about her behavior
  - "Up and down" we don't know what provokes her
  - Uncontrollable tantrums, rage, can even hit others during tantrums (put a hole in the wall)
  - Hypersensitive to fabrics, texture, very difficult getting dressed
  - Obsessive with certain things (shoes have to be just the right way)

Parents at wits end – daycare refusing her. What is wrong with her? With them?

Is it ADHD? Is it autism spectrum disorder? Could it be related to cCMV?

SECOND-LINE ASSESSMENT DEVELOPMENTAL PEDIATRICS

*Developmental pediatrician within the infectious diseases division (with a an occupational therapist & dedicated nurse practitioner)

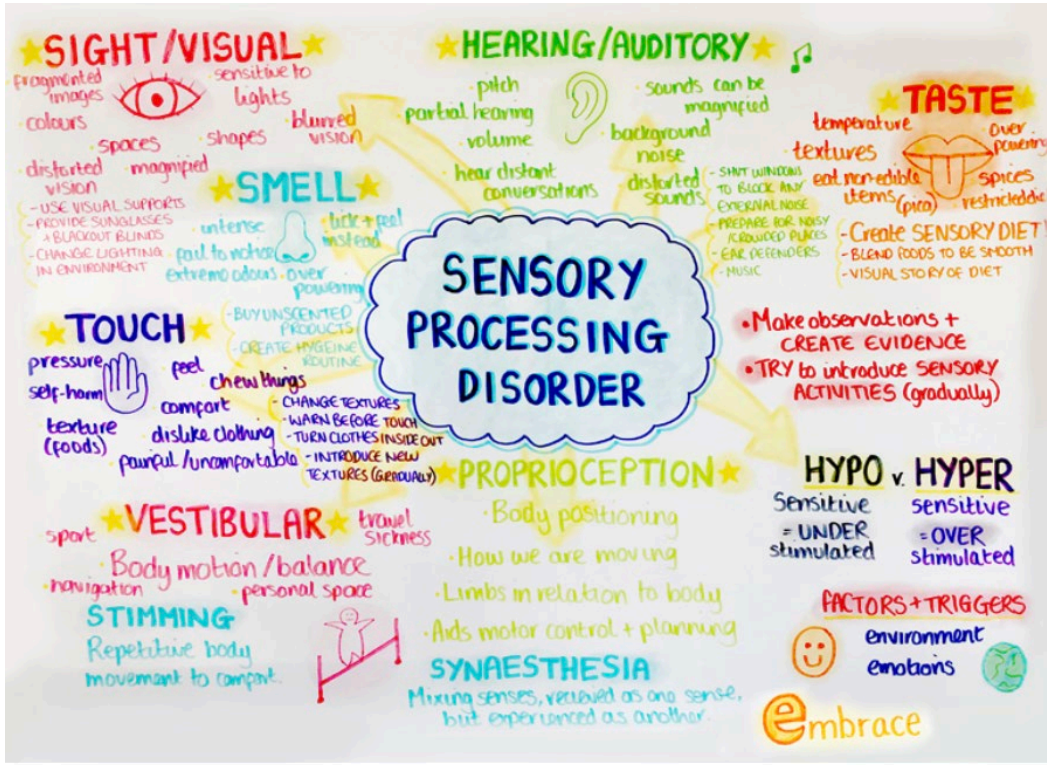
*Expertise: International adoption (attachment disorders), substance use pregnancy, HIV, Hepatitis C exposures

Diagnosis

- ADHD
- Sensory integration disorder (Sensory processing disorder)+++ with secondary dysregulated behavior

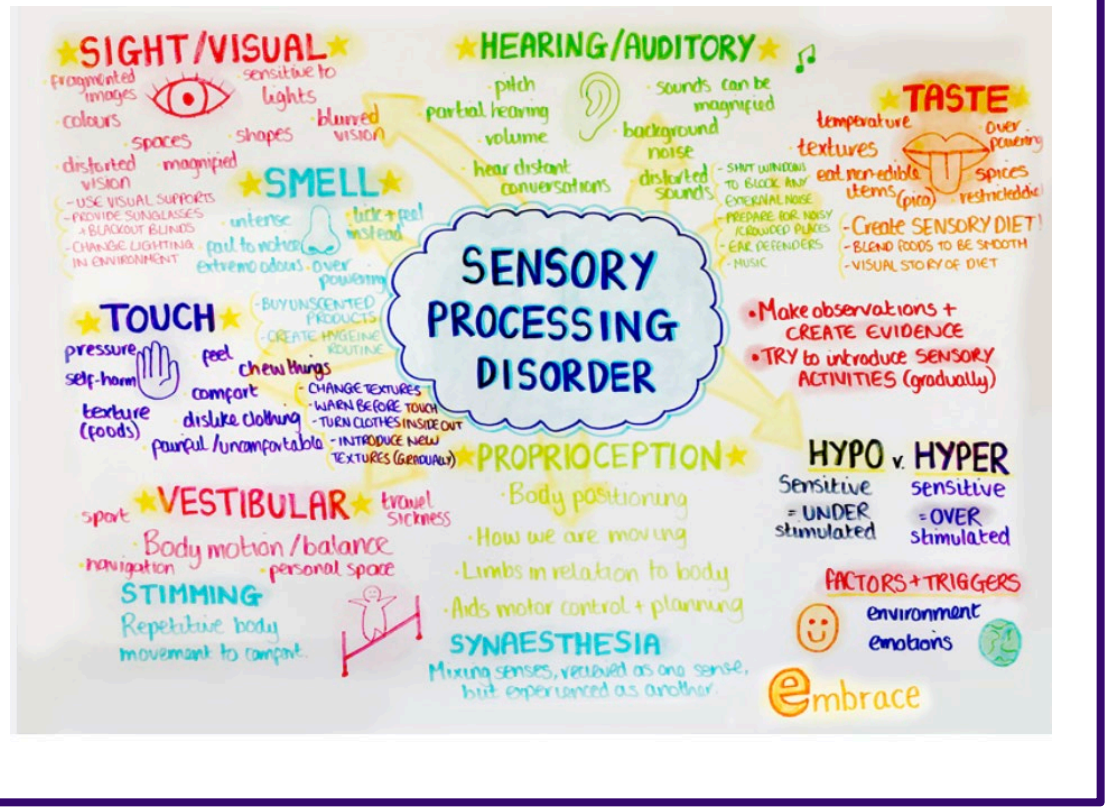
Question: Does CMV affect the senses? What parts of the brain does it involve?

SENSORY INTEGRATION (PROCESSING) DISORDERS 101



- Sensory Processing Disorder (SPD) is a condition in which the brain has difficulty receiving and responding to information that comes in through the senses.
- People with SPD may be oversensitive to sensory input, undersensitive, or both.
- This can affect any of the senses, including sight, sound, touch, taste, and smell.

SENSORY INTEGRATION (PROCESSING) DISORDER



1. **Sensory Modulation Disorder:** Difficulties regulating responses to sensory stimuli. Individuals may be oversensitive (hyperresponsive), under-sensitive (hyporesponsive), or seeking sensation (seekers).
2. **Sensory Discrimination Disorder:** Difficult in accurately **interpreting sensory** stimuli. Individuals might have trouble distinguishing between similar sensations, such as different textures or sounds.
3. **Sensory-Based Motor Disorder:** This affects the ability to **plan and execute movements** in response to sensory input. Individuals might have poor balance and coordination, and they may struggle with activities like riding a bike or tying shoelaces.

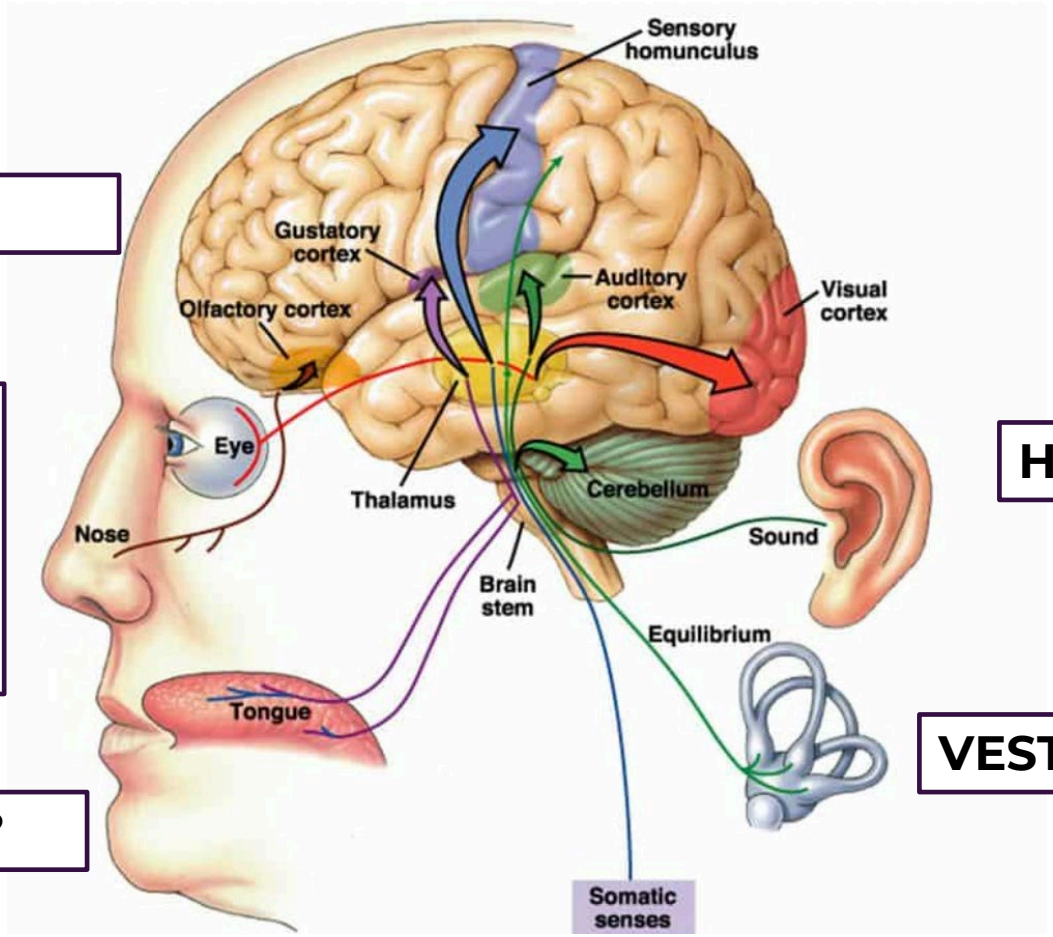
SENSORY INPUT AFFECTED IN CCMV

VISUAL

OLFACTORY

Lazarini et al: 10.1523/JNEUROSCI.0740-18.2018

Francois et al, 2022::10.1007/s00431-022-04375-1



HEARING

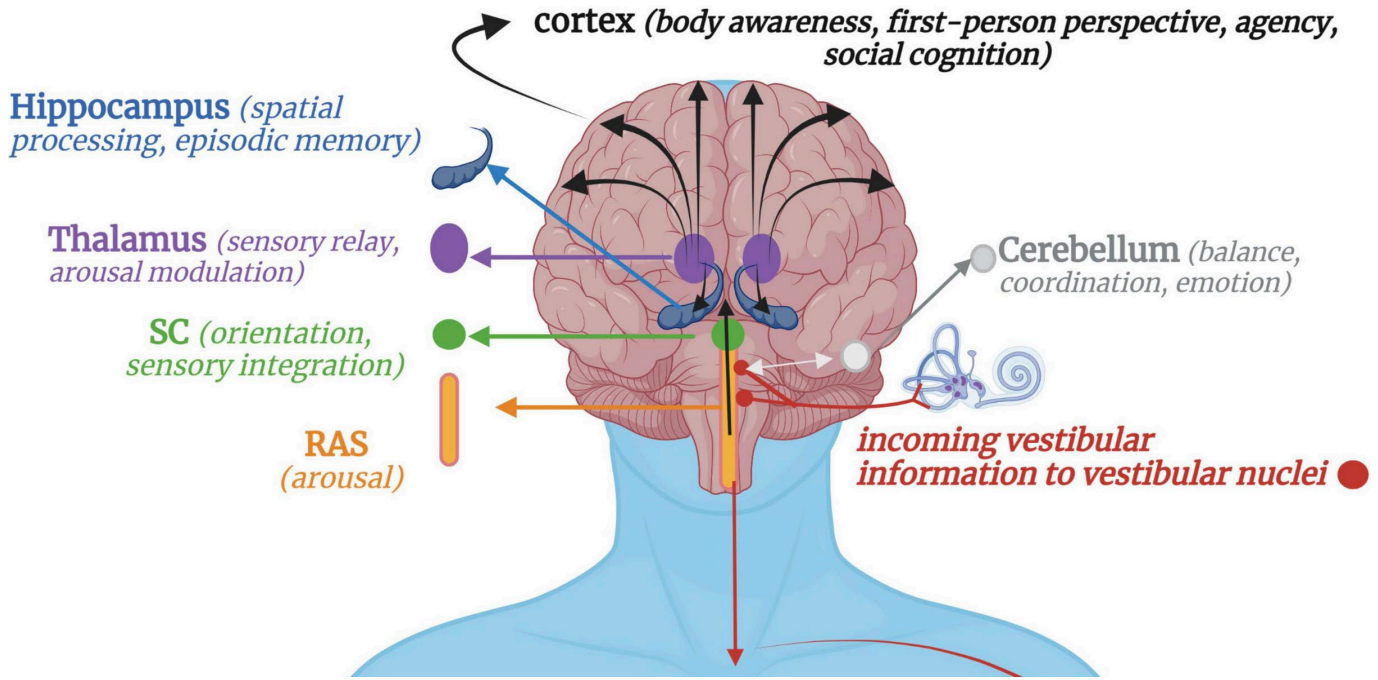
VESTIBULAR

TASTE?

SENSORY PROCESSING AFFECTED IN CMV

*STRUCTURAL CHANGES

*INFLAMMATORY CHANGES (SIGNALLING PATHWAYS)



HTTPS://WWW.INHA.IE/SENSORY-PROCESSING-DISORDER/

Sensory	Symptoms
Auditory	· Responds negatively to unexpected or loud noises · Holds hands over ears · Cannot walk with background noise · Seems oblivious within an active environment
Visual	· Prefers to be in the dark · Hesitates going up and down steps · Avoids bright lights · Stares intensely at people or objects · Avoids eye contact
Taste/Smell	· Avoids certain tastes/smells that are typically part of children's diets · Routinely smells nonfood objects · Seeks out certain tastes or smells · Does not seem to smell strong odors
Body Position	· Continually seeks out all kinds of movement activities · Hangs on other people, furniture, objects, even in familiar situations · Seems to have weak muscles, tires easily, has poor endurance · Walks on toes
Movement	· Becomes anxious or distressed when feet leave the ground · Avoids climbing or jumping · Avoids playground equipment · Seeks all kinds of movement and this interferes with daily life · Takes excessive risks while playing, has no safety awareness
Touch	· Avoids getting messy in glue, sand, finger paint, tape · Is sensitive to certain fabrics (clothing, bedding) · Touches people and objects at an irritating level · Avoids going barefoot, especially in grass or sand · Has decreased awareness of pain or temperature

IF IN CCMV

SENSORY INPUT AFFECTED
+

SENSORY PROCESSING AFFECTED

=

RESULTING OUTPUT?

Inattention and Hyperactivity in Children with Symptomatic and Asymptomatic Congenital Cytomegalovirus

J Dev Behav Pediatr 40:743–750, 2019

Congenital Cytomegalovirus Infection in Children with Autism Spectrum Disorder: Systematic Review and Meta-Analysis

Maeyama K.. Nishimura N. J Autism Dev Disord. 2018 May;48(5):1483-1491.

APS European Society for Paediatric Research spr Society for Pediatric Research

www.nature.com/pr

Pediatr Res. 2023 May 24. doi: 10.1038/s41390-023-02639-6. PMID: 37225779.

SYSTEMATIC REVIEW

Check for updates

Neurodevelopmental outcomes of children with congenital cytomegalovirus: a systematic scoping review

Megan H. Pesch[1]✉, Clare S. Lauer[1,2] and Jason B. Weinberg[3,4]

TARGETED THERAPIES FOR BEHAVIORAL DISORDERS AMONG CHILDREN WITH CONGENITAL CMV INFECTION

METHODS

Women and Children's Infectious Diseases Centre brings hospital's experts into single, multidisciplinary team

Isaac Olson · CBC News · Posted: Sep 26, 2018 5:26 AM EDT | Last Updated: September 26, 2018

The Mother and Child Infectious Diseases Centre at Sainte-Justine Hospital will bring together all the hospitals' experts to offer expectant and new mothers and their babies multidisciplinary care. (Radio-Canada)

- Retrospective single-center study
- Medical records of children with cCMV followed in the CIME CMV clinic (Montreal) were reviewed between 2008-2022
- Inclusion criteria
  - Confirmed congenital CMV infection
  - Age >=4 years at time of review.

OUTCOMES

- ***Any developmental developmental or behavioral issues a****s recorded in the chart:*

Any of *cerebral palsy, global developmental delay, balance disorder, language delay, behavioral disorder, motor delay, oppositional disorder, obsessive disorder, language deficit disorder attention hyperactivity, spectrum disorder autistic.*

- *First line assessment:*
  - *Pediatrician (infectious diseases trained) +- community Peds OR family medicine*
    - *Reference to OT or PT if any doubts*
    - *Referral for comprehensive readaptation in infancy if severe*
    - *Referral to second-line developmental assessment if uncertain, difficult manage first-line diagnosis*

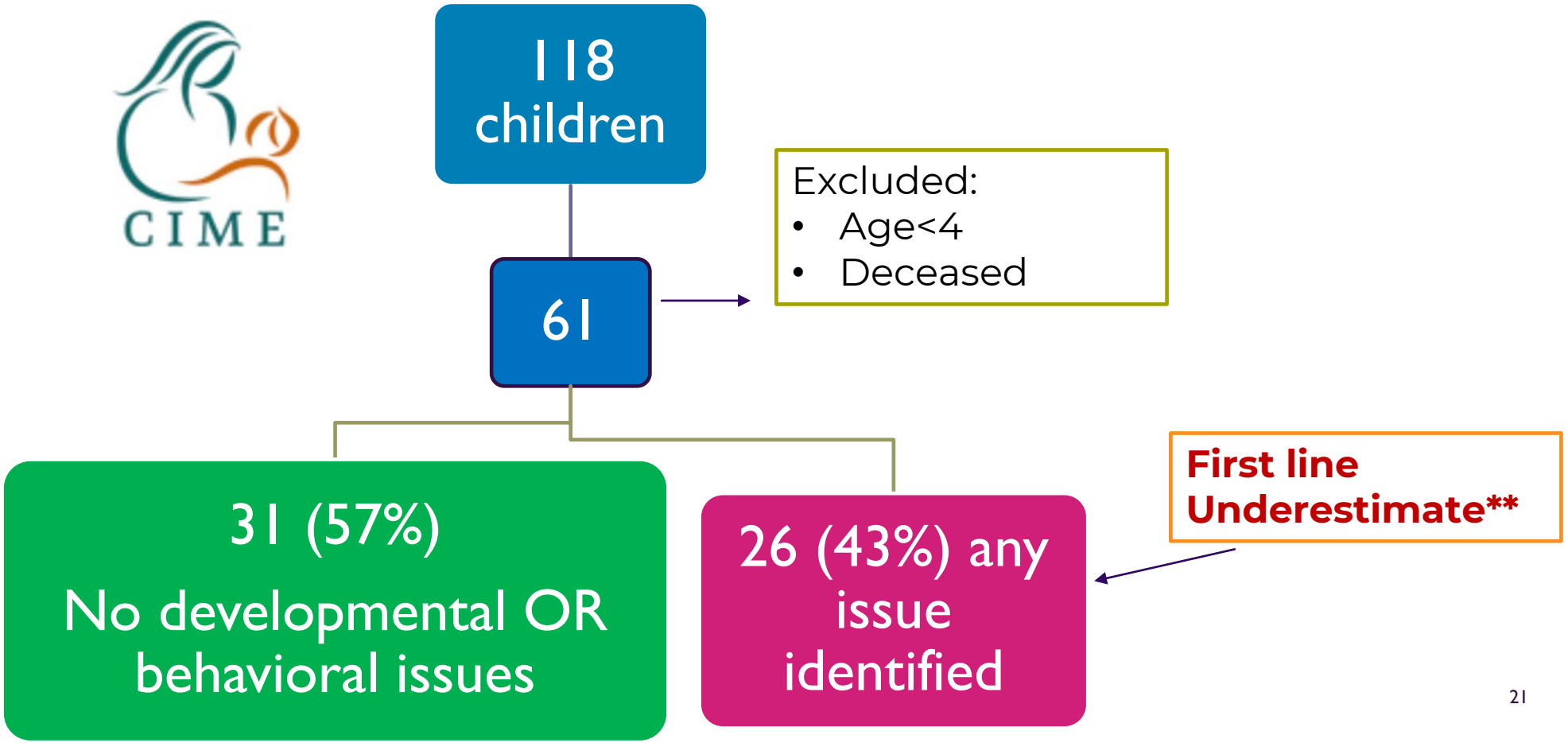
GENERAL CHARACTERISTICS OF THE COHORT

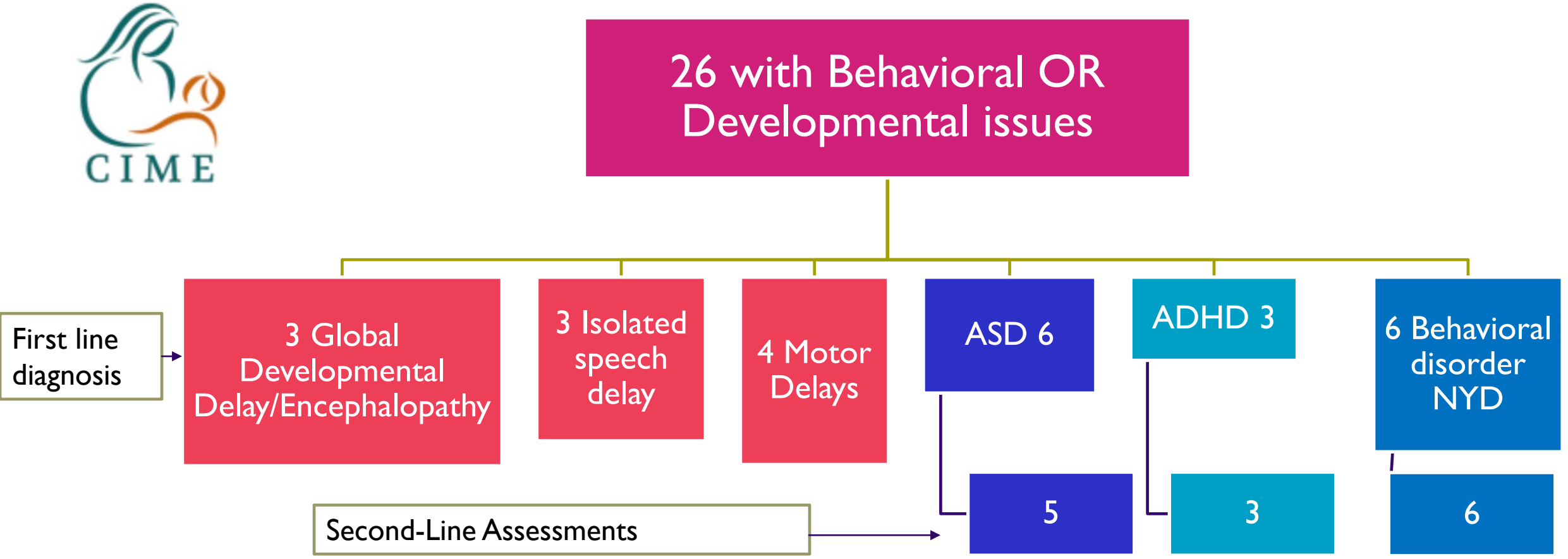
Reason for newborn testing	N= 118
Symptoms, n (%)	56 (47.4%)
Maternal serovonversion, n (%)	37 (31.3%)
Failed Hearing, n (%)	32 (27.1%)
HIV-exposed, n (%)	7 (5.9%)
NICU screening*, n (%)	1 (0.8%)

Characteristics	N= 118 patients
Female, N (%)	63 (53.3)
Gestational age (weeks), median	38
Birth weight (g), median	2885
Birth weight (g) ≤1500 (%)	3 (2.5)
Prematurity (<37 wk), n (%)	19 (15.9)
Prematury extreme (≤32 wk), n (%)	3 (2.5)
Symptomatic	93 (78.8%)

Heled –Akhiva et al, Int J.Neonatal Screening, 2023

DEVELOPMENTAL ASSESSMENTS




26 with Behavioral OR Developmental issues
First line diagnosis
3 Global Developmental Delay/Encephalopathy
3 Isolated speech delay
4 Motor Delays
ASD 6
ADHD 3
6 Behavioral disorder NYD
Second-Line Assessments
5
3
6

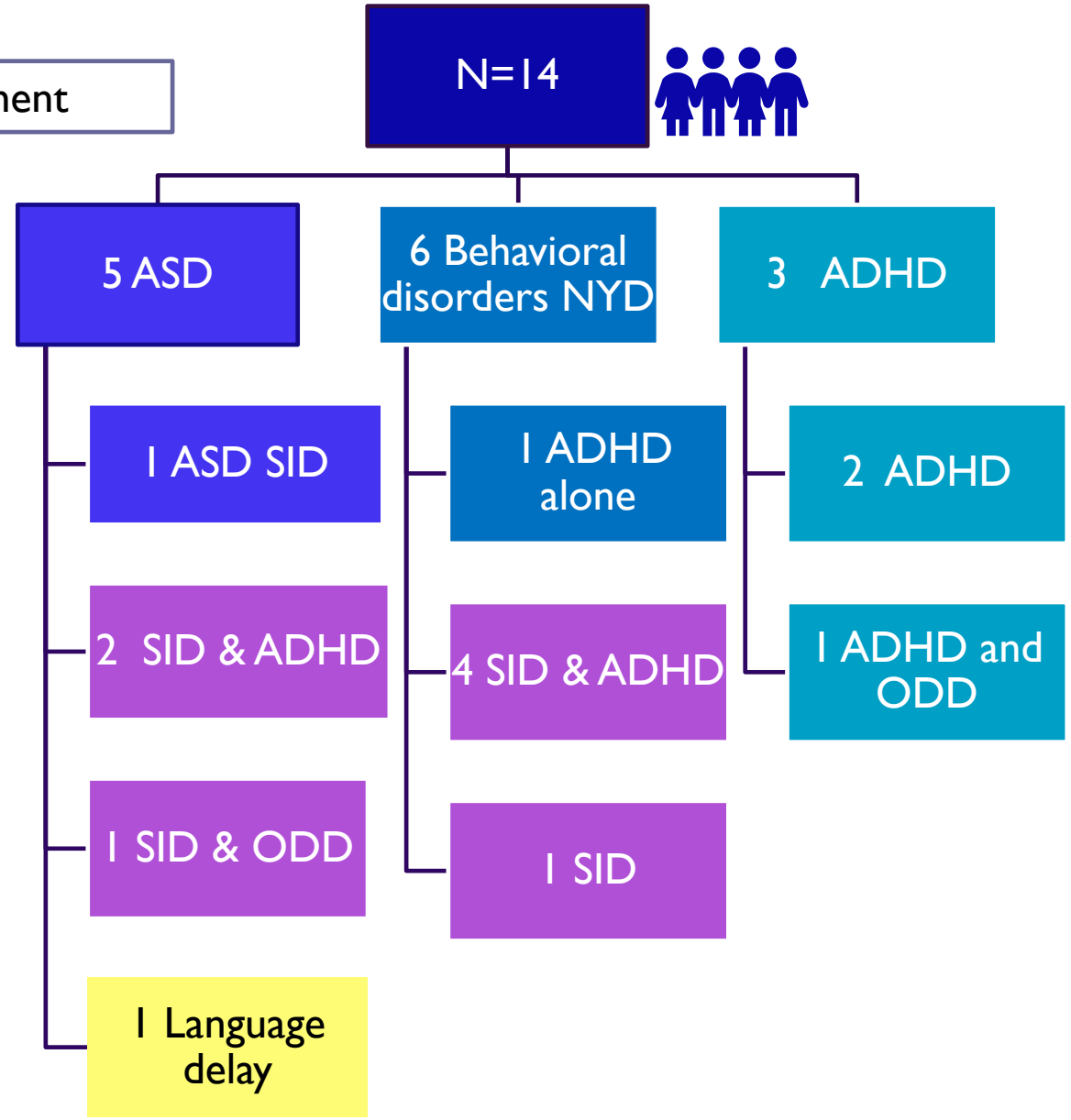
BEHAVIORAL DISORDER NYD – WHAT PARENTS REPORT: "OUR CHILD…"

Keeps getting kicked out of daycare
Highs and lows, cannot predict
Uncontrollable
Unprovoked rage, anger episodes
Too sensitive (touch, texture) and very picky
Always moving, jumping, putting self in danger

Second Line Developmental Assessment

First Line Diagnosis

Second Line Diagnosis



TARGETED THERAPIES /APPROACHES

Pharmacological:

Amphetamine-based psychostimulants

Methylphenidate-based psychostimulants

Non-psychostimulant selective alpha 2A adrenergic receptor agonist

Non-pharmacological

STIMULANT MEDICATIONS: FIRST-LINE

Amphetamine-based psychostimulants: Adderal, Vyvance

Methylphenidate-based psychostimulants: Biphentin, Concernta, Ritalin

- First line therapy for ADHD (long-acting stimulant)
- Increase neurotransmitter levels (dopamine and norepinephrine) which are lacking, especially in pre-frontal cortex
- **Allows “the sound in”**

NON-PSYCHOSTIMULANT SELECTIVE ALPHA-2 A ADRENERGIC RECEPTOR AGONIST: SECOND-LINE

- Intuniv (Guanafacine), Clonidine

- Strengthens postsynaptic α2A adrenoceptors in the midbrain and pyramidal cells of the prefrontal cortex → strengthens connections, enhances neuronal firing and increases top-down control
- "**Fine tunes the sound" so its not just "noise"**
- Improves prefrontal cortical functions
- **Role in dysregulated behaviour**

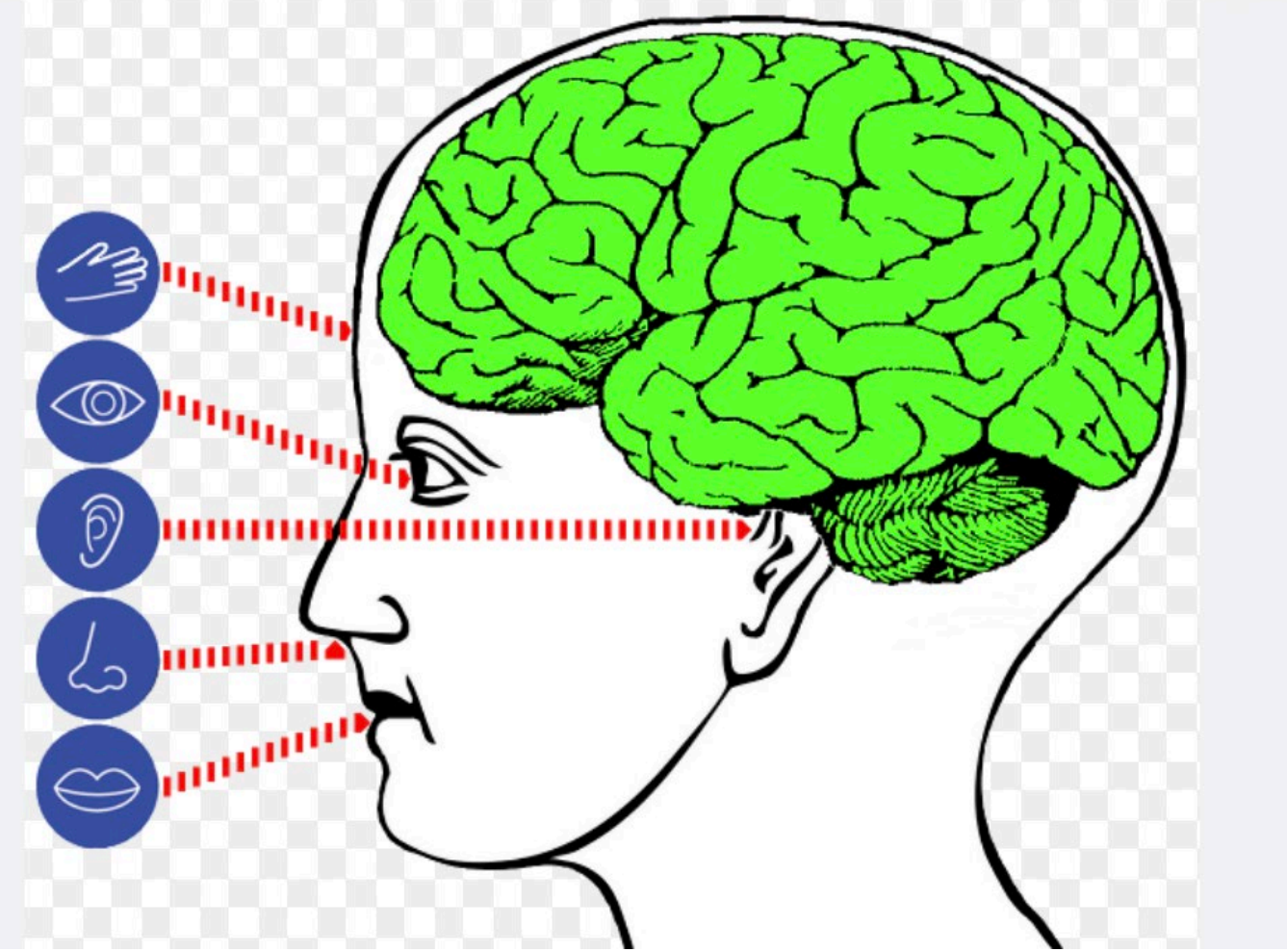
SENSORY INTEGRATION DISORDER PHARMACOTHERAPY

- Treatment with psychostimulant alone (for ADHD) could worsen behavior if there is associated emotional dysregulation, sensory integration disorders
  - "Amplifying the noise without allow it to be tuned"
  - Increase rage and aggression
- Addition of an Alpha 2 agonist helps regulate and essential to ADHD and Autism spectrum with associated SID
- Recognizing patterns of sensory processing difficulties in children with cCMV with these standard diagnoses (ADHD, Autism) can help tailor pharmacological therapy

	First line diagnosis	Final Diagnosis	Pharmacological interverntion
1	Autism and ADHD	SID & AHDH	Biphentin, **INTUNIV**, Mirtzapine
2	ADHD	ADHD and ODD	Vivance, **INTUNIV**, prozac
3	Behavioural disorder	ADHD	Biphentiin
4	Behavioural disorder	SID	None
5	Behavioural disorder	SID and ADHD	Vivance, **INTUNIV**
6	Autism	SID AND ADHD	Biphentin, **INTUNIV**
7	Autism	SID and ODD	None
8	Autism	SID and Autism	None
9	ADHD	ADHD (Impulsive)	None
10	Behavioural disorder	SID and ADHD	Vivance, **CLONIDINE**, Mirtazapine
11	ADHD	ADHD	Biphentin
12	Behavioural disorder	SID an ADHD	Ritalin, **CLONIDINE**
13	Behavioural disorder	SID and ADHD	Biphentin, **CLONIDINE**
14	Autism	Isolated language disorder	None

NON-PHARMACOLOGICAL INTERVENTIONS, (OCCUPATIONAL THERAPY) EXAMPLES

Touch	Infancy: Skin to skin, massaging (hands, feet) Childhood: Play with textures Weighted blankets, pressure garments
Vestibular	Infancy: Rocking chair Childhood: Hammock, swing School: Mobile cushion
Proprioception	Jumping ropes Dance classes
Hearing	Environmental modification Noise habituation
Vision	Newborn: Avoid all cell/screens with breastfeeding, holding Childhood: Natural environment vs. screens



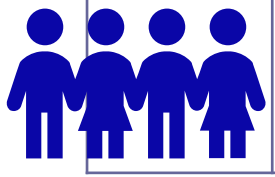
FUTURE DIRECTIONS: EVALUATING HOW THE CMV AFFECTED CHILD PROCESS THEIR ENVIRONMENT

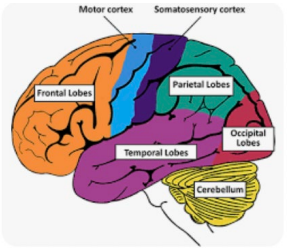
CURRENT EVALUATIONS FOR CCMV

	Diagnosis	Neuroimaging	Hearing	Vision
1	SID & AHDH	Intracranial/periventricular calcifications	SNHL	N
2	ADHD	N	SNHL	N
3	ADHD	Intracranial/periventricular calcifications cystic abnormalities	N	N
4	SID	N	N	N
5	SID and ADHD	Intracranial/periventricular calcifications	SNHL	N
6	SID AND ADHD	Intracranial/periventricular calcifications cystic abnormalities	SNHL	N
7	SID and ODD	Ventriculomegaly	N	N
8	SID and Autism	Intracranial/periventricular calcifications , ventriculomegaly	N	Right eye fibrosis
9	Impulsive	N	N	N
10	SID and ADHD	Intracranial/periventricular calcifications , ventriculomegaly	SNHL	N
11	ADHD	N	SNHL	N
12	SID an ADHD	N	N	N
13	SID and ADHD	N	SNHL	N
14	Isolated language disorder	Lenticulostriate vasculopathy	SNHL	N

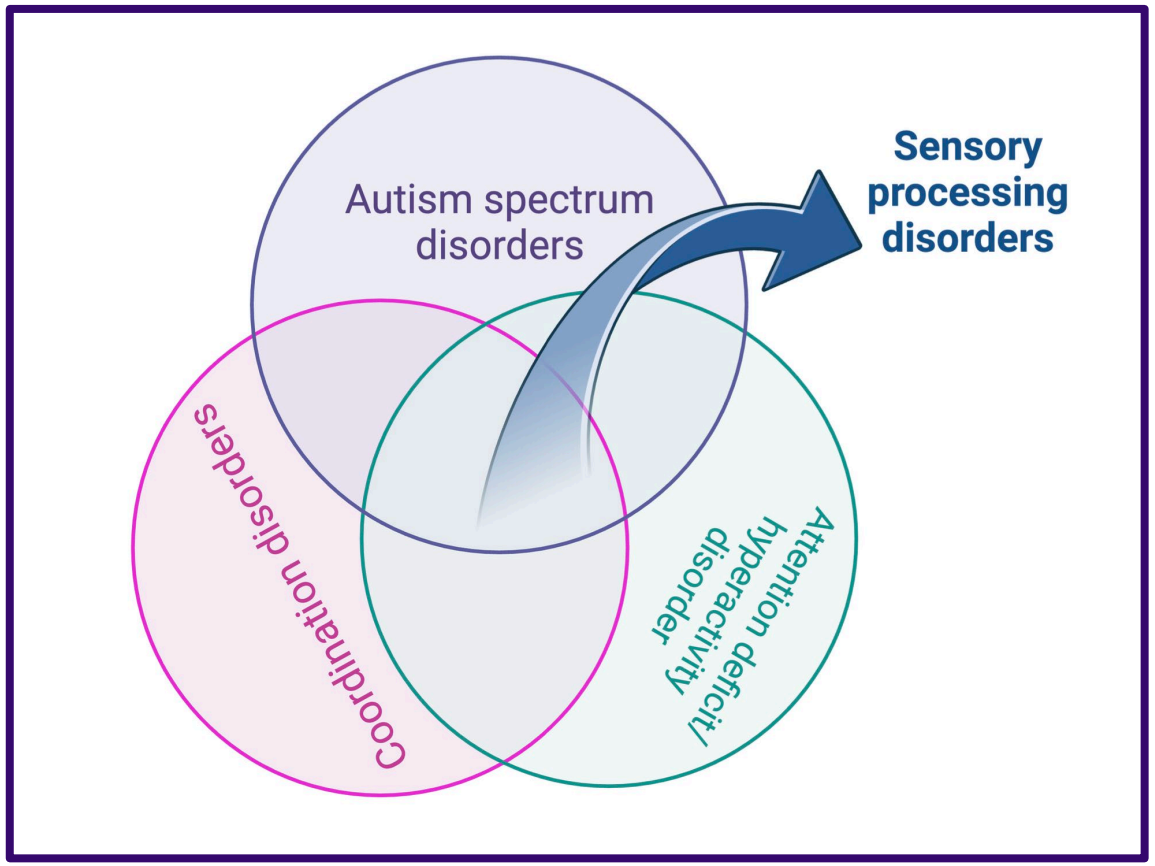
FUTURE DIRECTIONS:
SYSTEMATIC (SENSORY) EVALUATION OF CHILDREN WITH CCMV

	Hearing	VIsion	Olfactory	Vestibular	Proprioreception	Brain involvement





SENSORY PROCESSING DISORDER – AAP: CAUTION

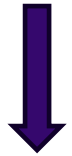


- Unclear whether children who present with findings described as sensory processing difficulties have an actual **"disorder"** of the sensory pathways or whether these deficits represent differences associated with other developmental and behavioral disorders (no DSM diagnosis)
- **The diagnosis of ASD is key to obtain/maintain services and support environment**
- Consider sensory processing issues when maladaptive behavior becomes a problem for the child
  - **ADHD**: Pharmacological treatment with adjuvant non-stimulant medicants
  - **ASD:** Potential for behavioral support therapy

Council on Children with Disabilities; American Academy of Pediatrics; Pediatrics. 2012 Jun;129(6):1186-9.

FUTURE RESEARCH

- Better define the pathogenesis of CMV on the developing brain and senses
- Better quantify processing challenges: Proprioception, olfactory, functional neuroimaging



Better respond to maladaptive behaviors (non- pharmacological and pharmacological)

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CMV CANADA

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