Neuropsychiatric features of OMAS

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Introduction

- Neuropsychiatry
- Behavioral phenotypes
- Compare and contrast with other neuropsychiatric disorders
- Case samples
- Clinical considerations
- Discussion

Neuropsychiatry

- Definition:

‘The neuropsychiatrist is … ideally suited to evaluate and treat patients who have abnormalities in perception, cognition, emotion, and/or behavior due to a known psychiatric or neurologic disorder; due to the simultaneous presence of, or interaction between, psychiatric and neurologic disorders (or their treatments), and associated psychosocial elements; or due to an unknown underlying brain condition.’

-D. Silbersweig, *Neuropsychiatry and Behavioral Neurology Principles and Practice*, 2021

Neuropsychiatry

- Interested in understanding neuroanatomical correlates of behavior, emotion and thought
- Utilizing circuit-based and neurotransmitter-informed data for neuropsychiatric diagnosis and treatment
- Integration of therapeutic techniques
  - Psychotherapy
  - Medication management
  - Neurostimulation

Behavioral phenotypes

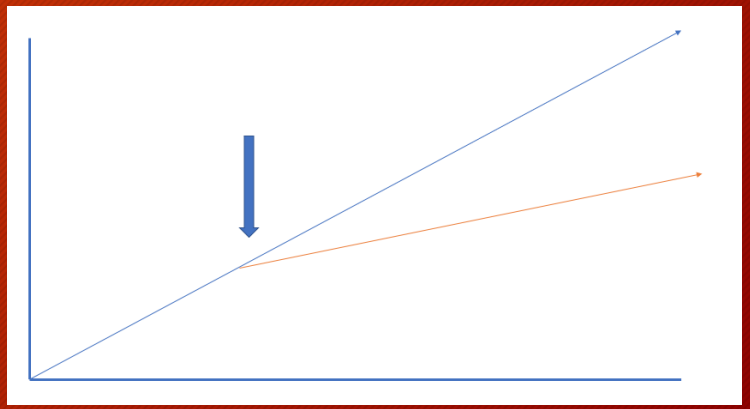
- What are the psychiatric profiles associated with a neuropsychiatric condition?
- Can we separate features of the pathophysiology of a disease from ancillary factors?
  - Trauma (illness, hospitalization, existential uncertainty, etc.)
  - Developmental impact of being a medically-ill child
  - Iatrogenic effects
- How can this drive treatment, especially where data is limited?
- How can anticipation of specific potential symptoms help us to prevent outcomes rather than manage them after-the-fact?

Regression and development

- Injury occurs in presence of ongoing development (single or repeated), not after reaching a static state
- Additional challenge of a dynamic disease process
- Un-related psychiatric/dev comorbidities versus sequelae
- Treatment-related sequelae
- Trauma and adjustment disorder
- Challenges with prioritization of

acute or life-threatening needs

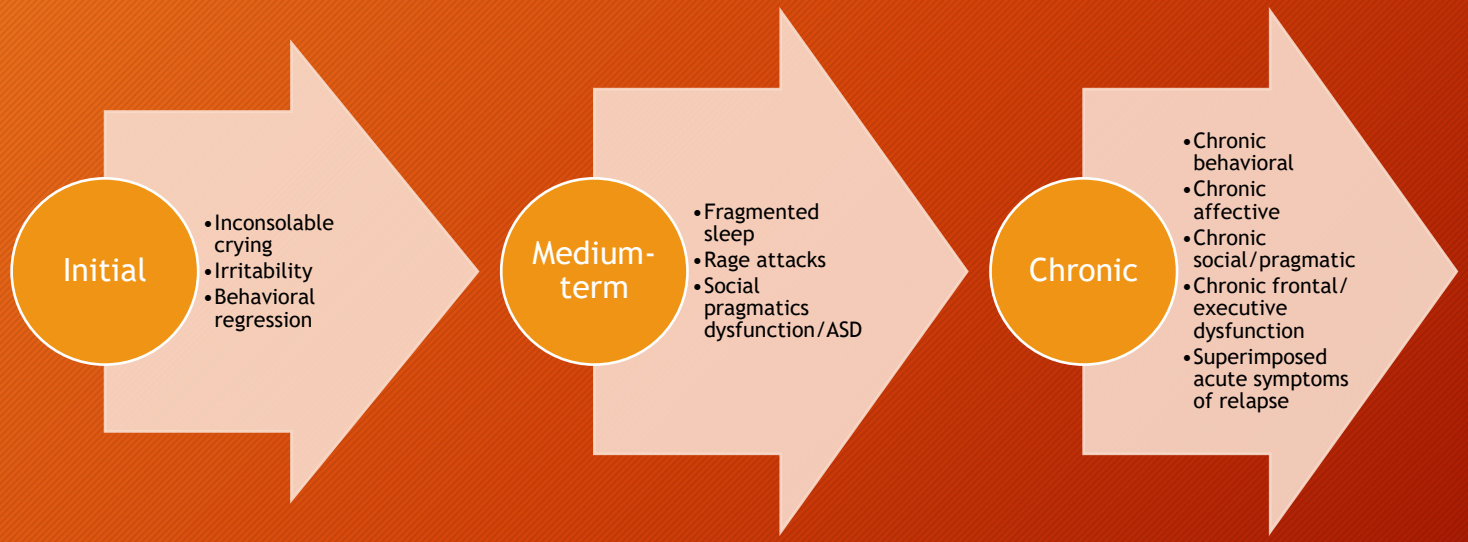
resulting in deferred psychiatric care



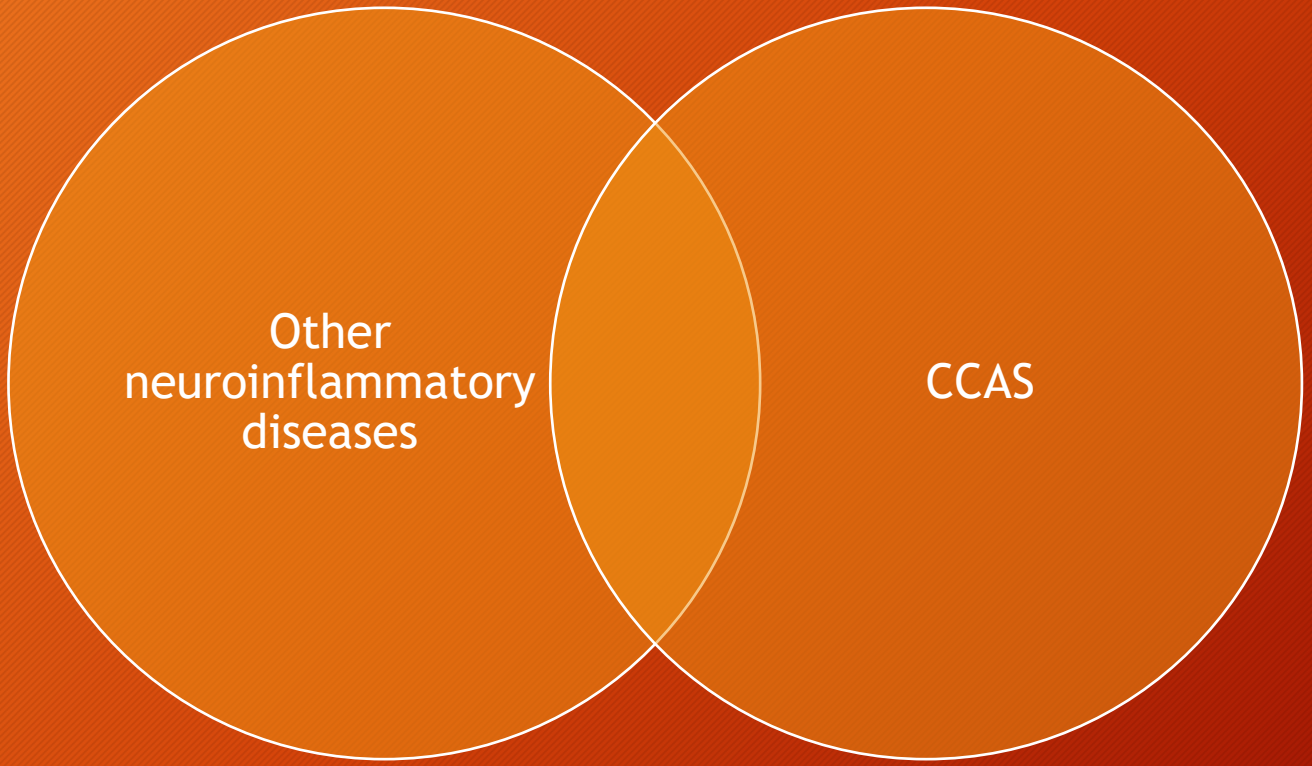
Neuropsychiatric features of OMAS

- Neurobehavioral
  - Insomnia
  - Irritability/inconsolability
  - “Rage attacks”
  - Frontal-executive dysfunction
  - Social pragmatics deficits/Autism spectrum disorder symptoms/attenuated ASD-like symptoms
  - Chronic mood/anxiety symptoms
  - OCD-like or repetitive behavioral symptom profile
- Neurocognitive
  - Language (expressive>receptive)
  - Frontal-executive
  - Working memory

Time course


Initial
•Inconsolable crying
•Irritability
•Behavioral regression
Medium-term
•Fragmented sleep
•Rage attacks
•Social pragmatics dysfunction/ASD
Chronic
•Chronic behavioral
•Chronic affective
•Chronic social/pragmatic
•Chronic frontal/executive dysfunction
•Superimposed acute symptoms of relapse

Potential models for behavioral phenotype



Shared and differentiating features

- Features which overlap many neuroinflammatory disorders
  - Neurocognitive features (frontal/executive dysfunction)
  - Language disorders (expressive>receptive)
  - Greater impact on productive than receptive language
  - Working memory deficits
  - Mood/anxiety disorders
- Features which overlap other cerebellar injuries
  - ASD-like features/social pragmatics deficits
  - Irritability, behavioral difficulties
  - Frontal-executive dysfunction
  - Anxiety
  - Sleep disturbance (e.g., autosomal dominant spinocerebellar ataxias)
- Features which overlap with acute cerebellar ataxia
  - Movement symptoms, but dearth of overlap with neurobehavioral symptoms
- Possibly idiosyncratic features
  - Prevalence of severe insomnia
  - Relative prevalence and severity of irritability compared with other features
  - Relative absence of psychosis or mania

Sequelae in pediatric neuroinflammatory diseases

Acute/initial course

- Neuropsychiatric
  - Psychosis
  - Mania
  - Agitation
  - Anxiety
  - OCD-like sx
- Neurocognitive
  - Language
  - Memory
  - Executive dysfunction
- Neurological
  - Delirium
  - Catatonia
  - Delirium
  - Movement disorder
  - Seizures

1/3 of children with AE have long-term psychiatric symptom

Cognitive features:

- Language deficit
  - Naming
  - Expressive/ receptive
- Memory deficit
  - Verbal
  - Visual
- Executive functioning
  - Problem solving
  - Inhibition
  - Planning
- Sustained attention

Psychiatric features:

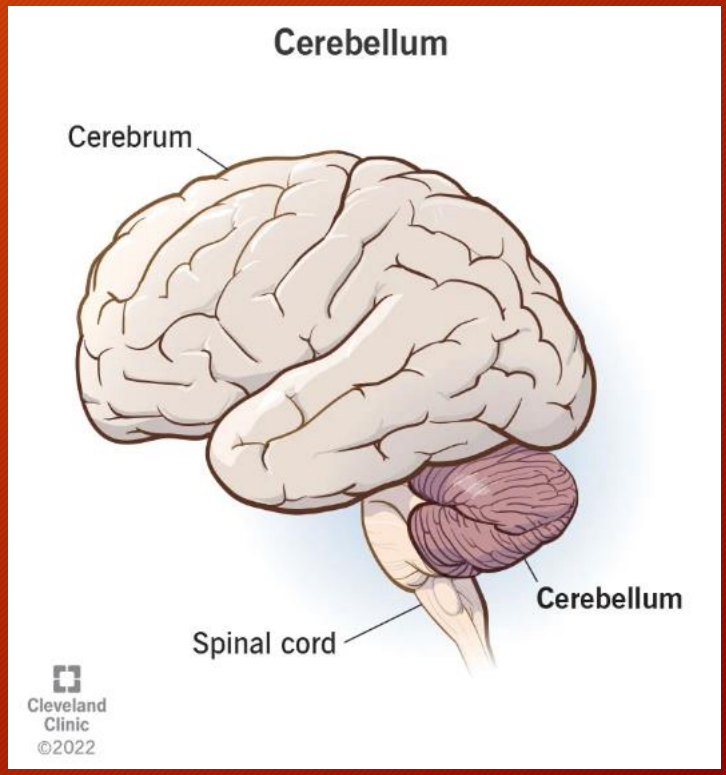
- Residual anxiety
- Inattention/impulsivity
- Attenuated psychosis
- Depression
- OCD

•Sometimes correlating with localization, sometimes not

Courtesy of V Ferrafiat

Theoretical underpinnings

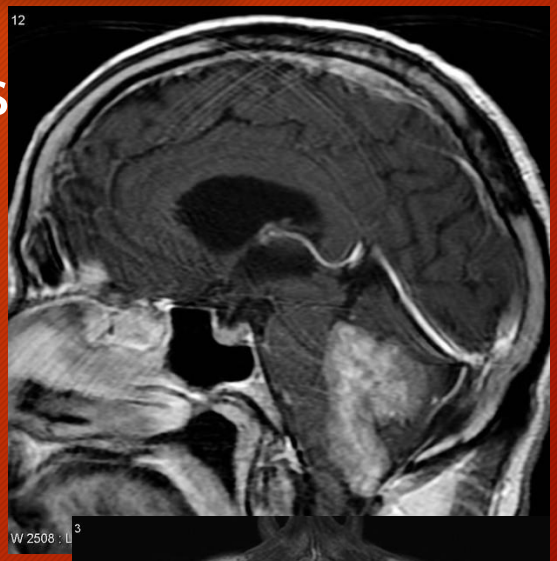
- Cerebellar Cognitive and Affective Syndrome (CCAS)
  - "Dysmetria of thought"
  - "Universal cerebellar transform"
    - "The cerebellum maintains behavior around a homeostatic baseline, automatically, without conscious awareness, informed by implicit learning, and performed according to context."

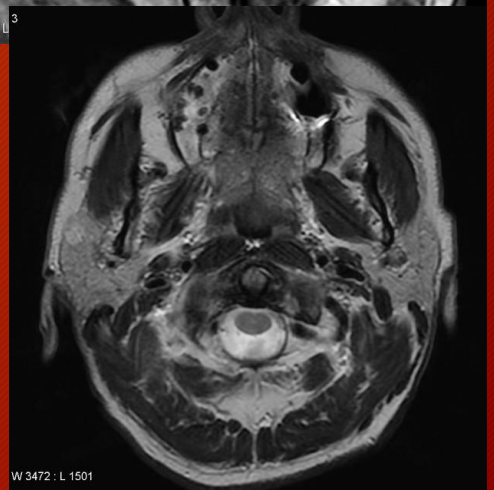


Schmahmann 2019

Broad range of diseases resulting in CCAS

- Post-resection cerebellar tumor patients ("posterior fossa syndrome")
- Degenerative cerebellar diseases
- Stroke
- Tumor
- Schizophrenia data
- ASD Data
- Etc.



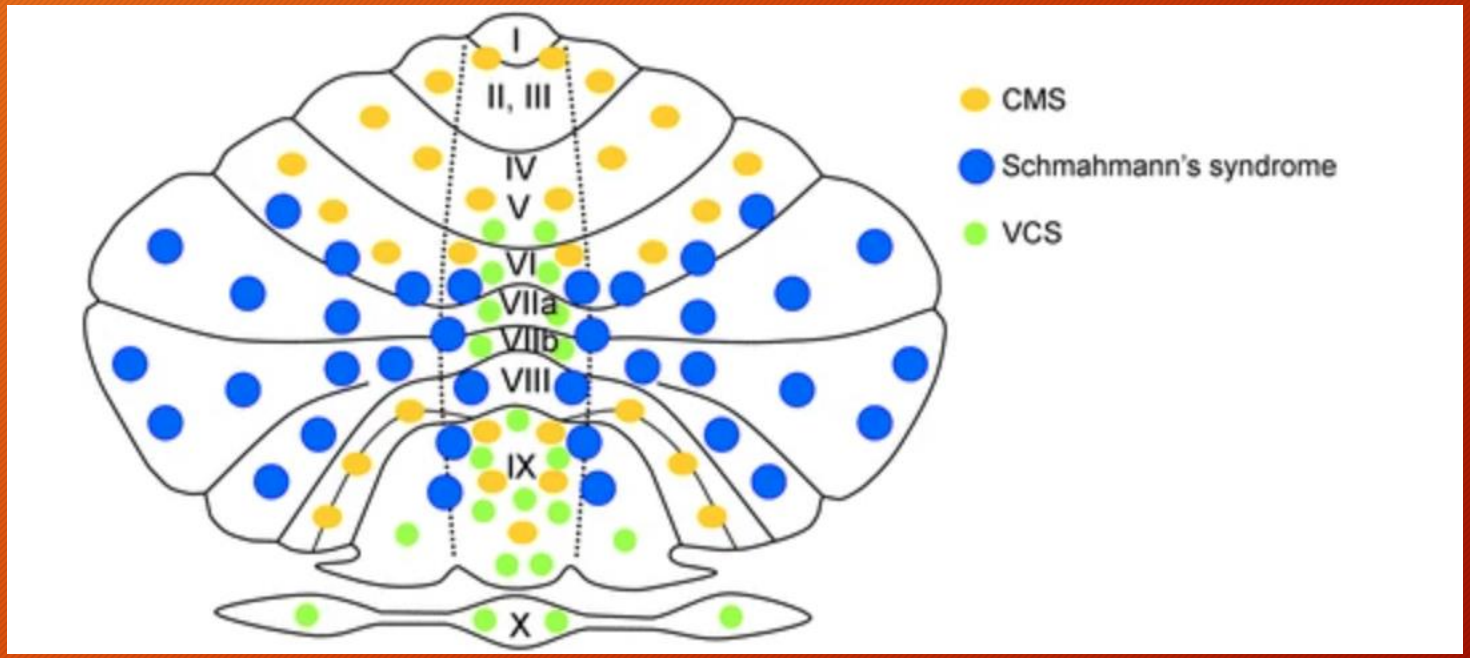


https://radiopaedia.org/articles/posterior-fossa-tumours

CCAS

Domains	Functions	
Executive Function	Planning Set-shifting Abstraction Working memory Verbal fluency	
Visuo-spatial	Visuo-spatial organization Visuo-spatial planning	
Personality/affect	Social inhibition Affective fullness	
Language	Prosody Grammatism Naming	

CCAS

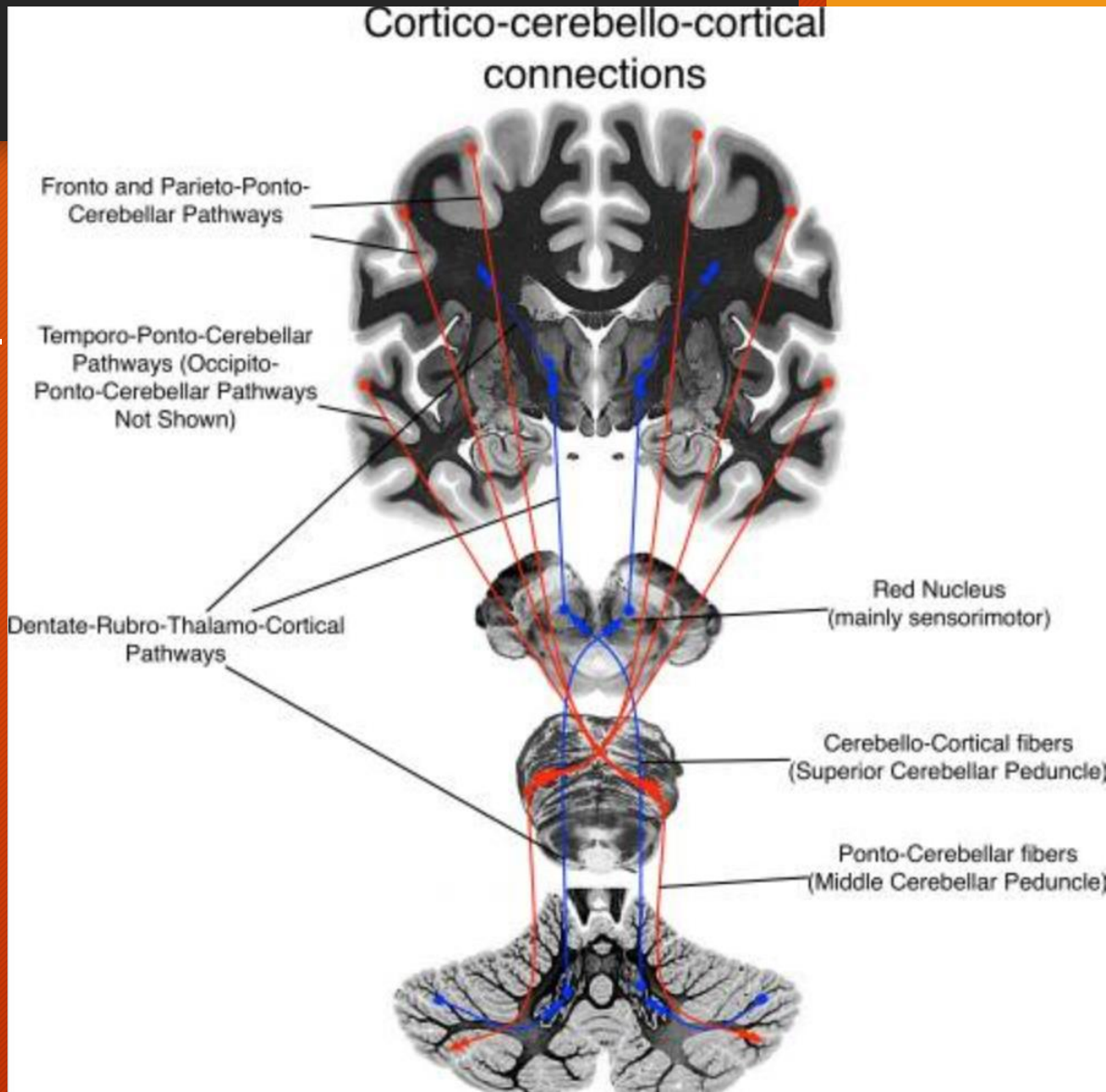


Yellow: Cerebellar motor syndrome
Blue: CCAS
Green: Vestibulo-cerebellar syndrome

Manto, M., Mariën, P. Schmahmann's syndrome - identification of the third cornerstone of clinical ataxiology. *cerebellum ataxias* **2**, 2 (2015). https://doi.org/10.1186/s40673-015-0023-1

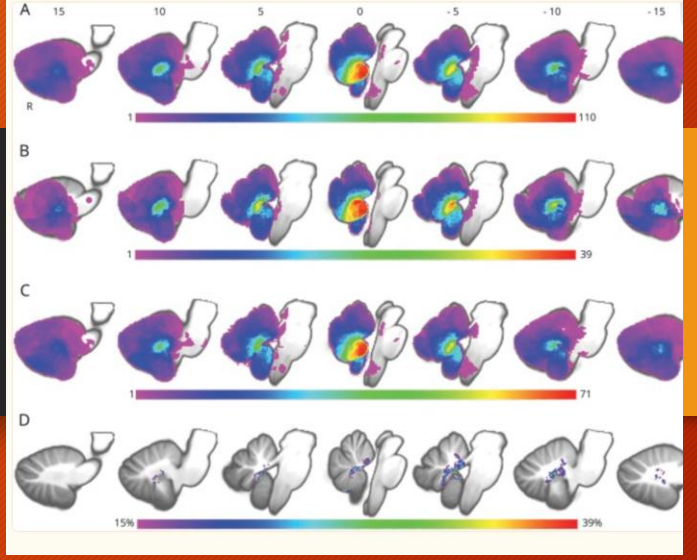
CCAS

- Lobules VI-IX
- Cerebello-thalamo-cerebro-cortical circuits (CTCCs)



Vias and Dick 2017

CCAS



- Postoperative CCAS findings
  - Mapping 195 post-surgical cerebellar tumor patients found CCAS strongly associated with cerebellar outflow tract lesions, “anatomic bottleneck”
  - Deep nuclei, superior cerebellar peduncles
- Lesion network mapping:
  - Functional connectivity studies shows mediodorsal nucleus of the thalamus
  - Associated with a range of PFC connections

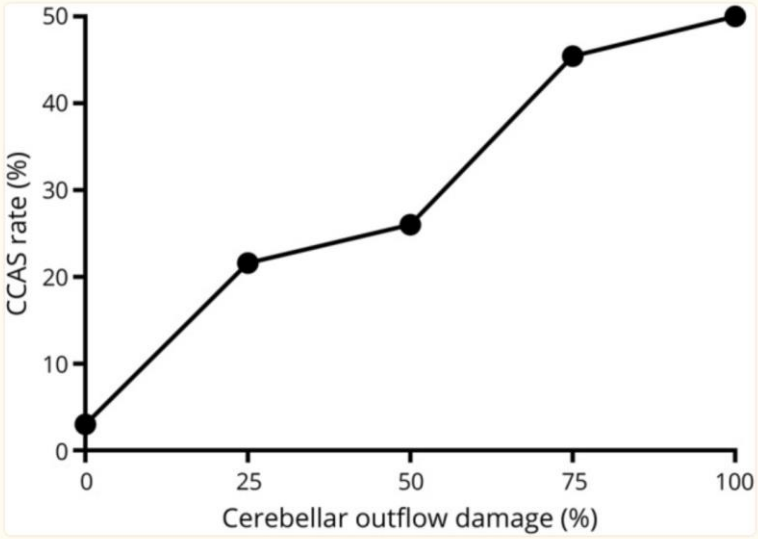


Figure 3

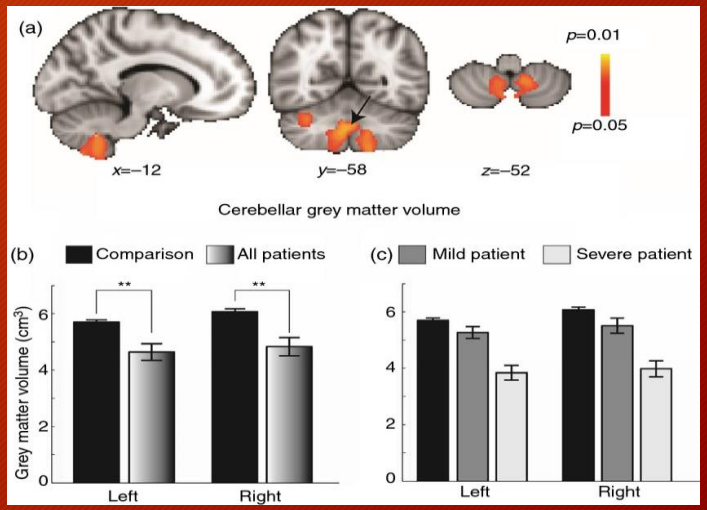
Risk of CCAS stratified by cerebellar outflow pathway lesion load

This figure demonstrates that cerebellar cognitive affective syndrome(CCAS) rates are higher as the proportion of cerebellar outflow damage increases. The number of participants with CCAS compared to those without CCAS was as follows: no cerebellar outflow damage CCAS = 1, no CCAS = 32; 0% to 25% damage CCAS = 16, no CCAS = 58; 25% to 50% damage CCAS = 13, no CCAS = 37; 50% to 75% damage CCAS = 10, no CCAS = 12; and 75% to 100% damage CCAS = 8, no CCAS = 8.

Albazron et al Pediatric postoperative cerebellar cognitive affective syndrome follows outflow pathway lesions.
Neurology. 2019 Oct 15;93(16):e1561-e1571.

CCAS

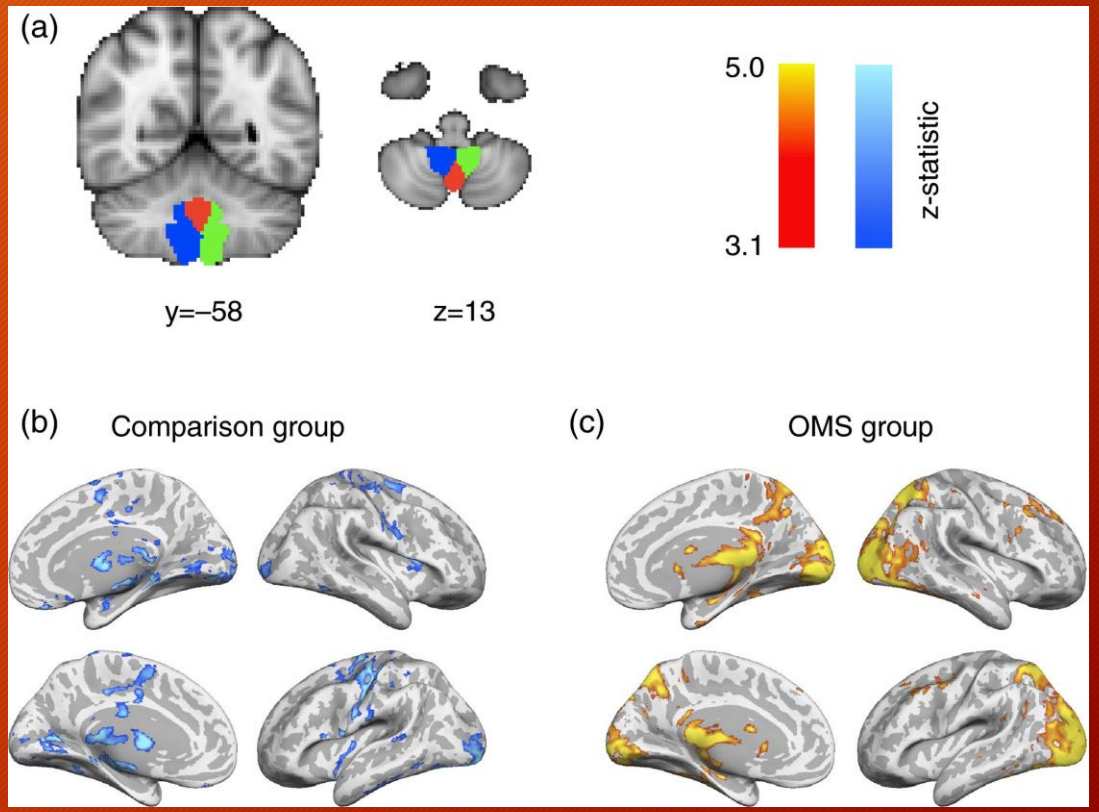
- Voxel-based morphometry demonstrates extensive reduction in cerebellar grey matter in OMS patients
- Reductions correlated with OMS scores
  - Flocculonodular lobes
  - Cerebellar vermis
- Increased mean diffusivity in cerebellar white matter tracts
  - Esp. middle cerebellar peduncle connecting cerebellum to pons
- Cerebral gray matter
  - Motor
  - Visual cortices



Anand G, Bridge H, Rackstraw P, Chekroud AM, Yong J, Stagg CJ, Pike M. Cerebellar and cortical abnormalities in paediatric opsoclonus-myoclonus syndrome. Dev Med Child Neurol. 2015 Mar;57(3):265-72.

OMAS and connectivity

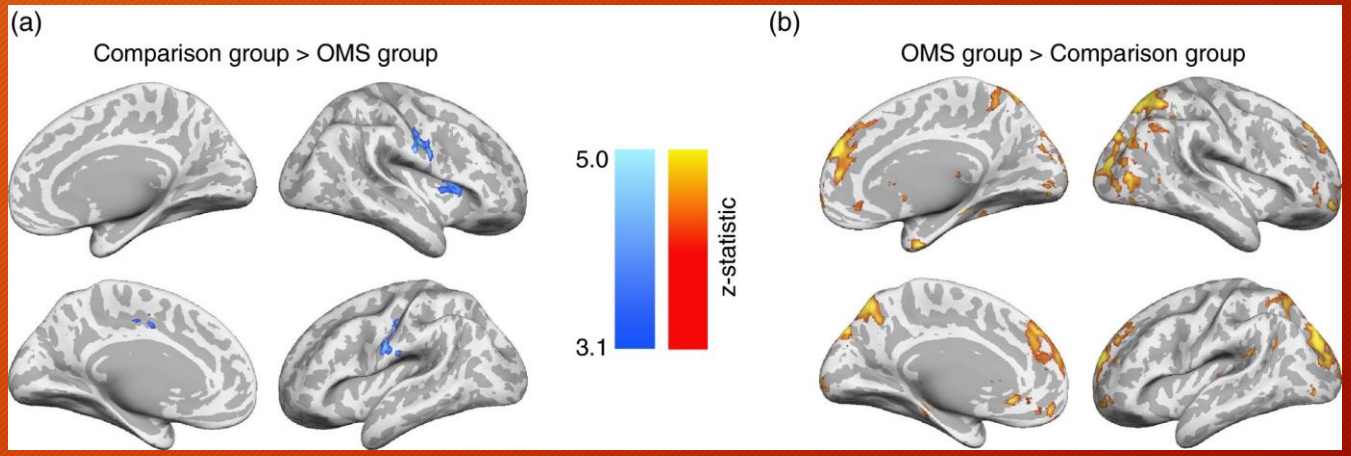
- Reduced connectivity between cerebellum and motor cortex.
- Increased functional connectivity between the cerebellum and parieto-occipital regions
- Suggests widespread involvement
- Directing of visual attention, mirrors some ADHD findings
- Similar to *Cerliani* et al findings in ASD



Develop Med Child Neuro, Volume: 59, Issue: 1, Pages: 98-104, First published: 23 September 2016, DOI: (10.1111/dmcn.13262)

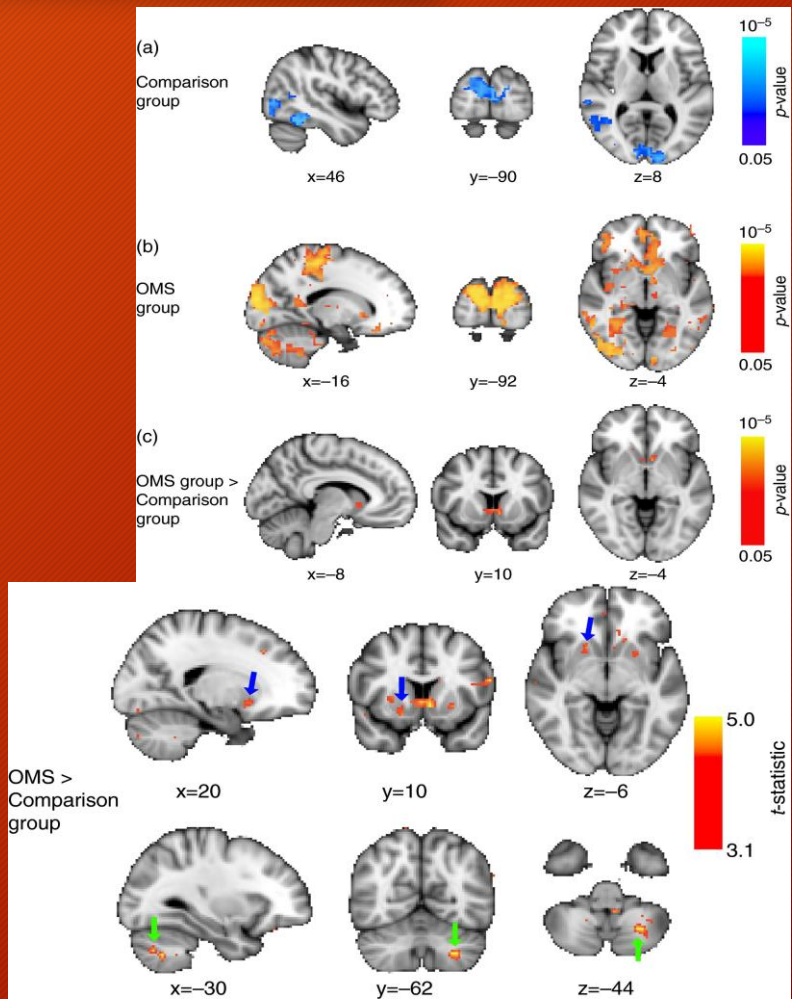
OMAS and connectivity

- “Additionally, there was considerably greater correlation of the frontal cortex with the cerebellum in OMS participants. The reason for this spectrum of correlated activity is not clear, although it was present in several participants rather than being driven by a single data set.”



OMAS and connectivity

- Independent component analysis identified visual network not represented in controls including frontal and parietal structures
- Reached significance in caudate nucleus
- Increased correlation between subcortical motor and cortical structures in ASD correlates with severity



CCAS

- Mediodorsal thalamus projects to
  - Anterior cingulate
  - Medial, lateral prefrontal cortices
  - Orbitofrontal cortex

  - Role in:
    - Cognitive control
    - Working memory
    - Decision-making
    - "Everyday tasks requiring rapid updating"
    - Particular focus on fluidity of cognitive operations
    - Role in cognitive symptoms in schizophrenia

Figure 2

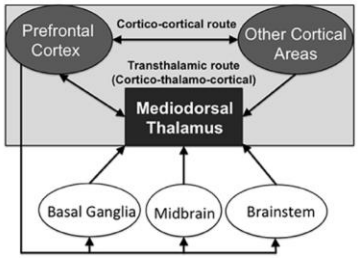
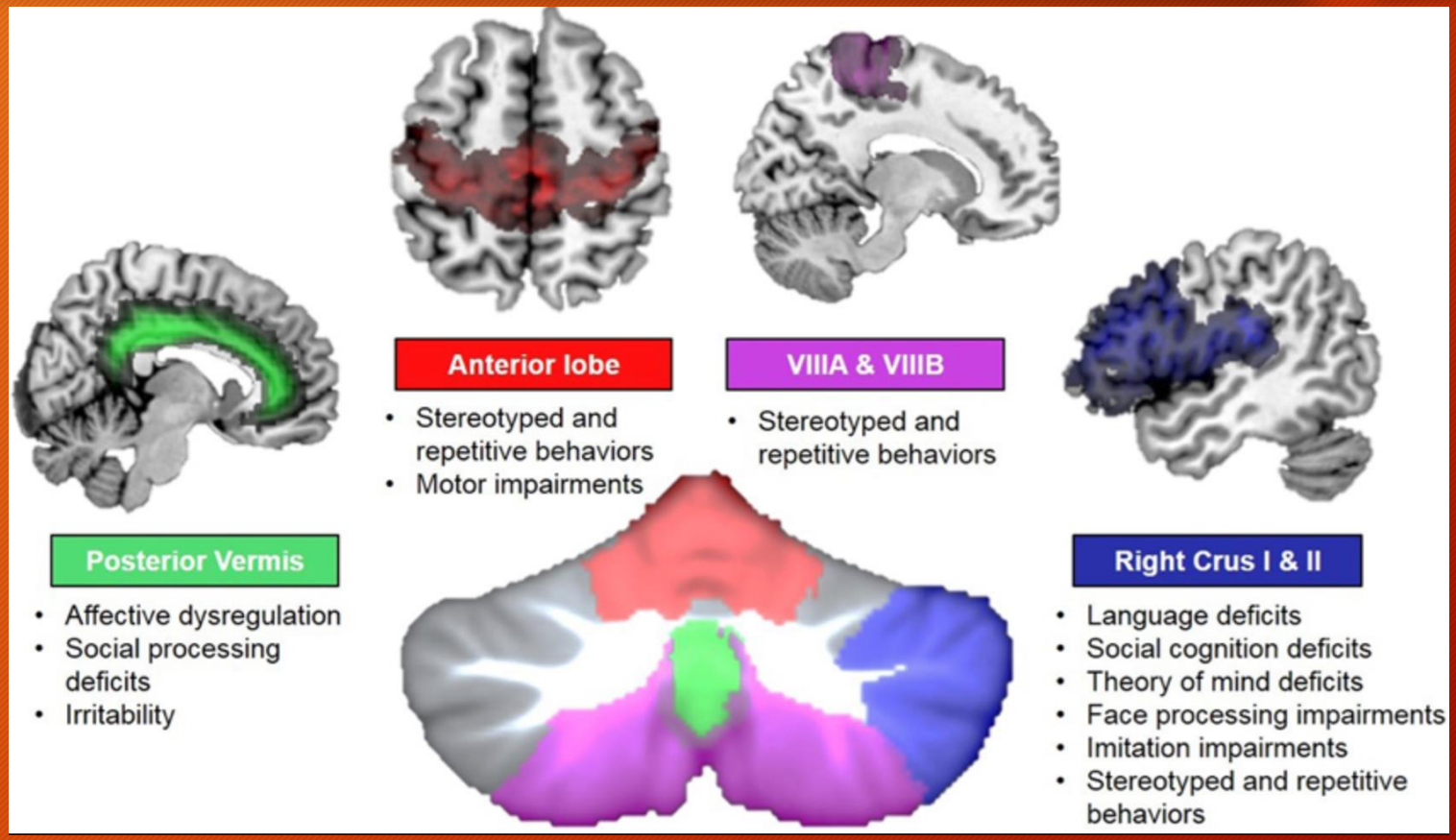


FIGURE 2. Schematic diagram showing the direct cortico-cortical routes of neural transmission and the indirect transthalamic (cortico-thalamo-cortical) routes of transmission, via the higher order thalamic nuclei. Neuromodulatory inputs from other interconnected brain structures regulate the transmission via the transthalamic route.

Ouhaz et al 2018

Cerebellar role in neurobehavioral symptoms



D'Mello and Stoodley 2015

Cerebellar role in social pragmatics

- Cerebellocorticopontine connections with important regions
  - Temporal lobe, VMPFC, amygdala (face processing)
- Altered face perception in SCA patients (D'Agita et al 2011) and deterioration in ToM in SCA progression (Moriarty et al 2016)
- ASD structural (Laidi et al 2015) and functional (Igelstrom et al 2017, Olivito et al 2017, Jack and Morris 2014, Jack et al 2017) data
- Etc.

Cases

Case 1

- 2yo male with following history
  - Ataxia for 1 month
  - Severe irritability and insomnia for 1 week
  - On exam, extremely irritable and constantly crying, opsoclonus and ataxia
  - Neuroblastoma detected and resected
  - Despite tumor resection, steroids, IVIg and rituximab, severe irritability and insomnia persisted
  - Treated with melatonin, clonidine and gabapentin with improvement

Case 2

- 16yo female with following history
  - Paraneoplastic OMAS onset at 2yo
  - Initial symptoms included irritability and insomnia
  - Multiple OMAS relapses
  - Treatments: tumor resection, steroids, IVIg, and rituximab
  - Currently, no active OMAS symptoms or signs
  - Serial neuropsychology with average IQ and no regression, but difficulties in language retrieval, planning, organization, and integration, and slow processing speed
  - Has school accommodations
  - Also has mild to moderate anxiety, currently in therapy

Case 3

- 14yo male with following history
  - Non-paraneoplastic OMAS onset at 1yo
  - Received inconsistent steroids and IVIg
  - Multiple OMAS relapses
  - At age 4yo, had ataxia and severe expressive language delay, unable to put 2 words together
  - Improved with ACTH and IVIg but remained with language delay: phrases age 9, sentences age 12
  - Neuropsych testing with IQ 50
  - Noted to have repetitive behaviors including hand flapping
  - Impaired social skills; tried to make friends but difficulty with social communication and cues
  - Met DSM criteria for ASD

Case 4

- 25yo female with following history
  - Paraneoplastic OMAS onset at 1yo
  - Multiple OMAS relapses
  - Treatments included steroids, ACTH, IVIg, and cyclophosphamide
  - Serial neuropsychological testing showed regression in IQ from above average to borderline
  - At age 13, developed auditory and visual hallucinations, diagnosed with psychotic disorder and treated with antipsychotics
  - At age 25, relatively stable but continues to require antipsychotic medication

Psychopharmacology in neuroinflammatory diseases

- Treatments and their impact on psychiatric symptoms
  - Disease-modifying agents
  - Modifiers of underlying pathophysiological circuitry
  - Symptom modifying agents
  - Sedation
  - Behavioral and psychotherapeutic targets

Disease modifying agents

- Modulating the underlying illness (e.g., immunosuppression) may halt or reverse psychiatric symptoms to varying degrees
- Example:
  - Tumor removal and immunomodulatory therapy in anti-NMDA receptor encephalitis
    - +/- adjuvant psychotropic medication or ECT
  - Immunomodulatory therapy in neuropsychiatric SLE
  - Discontinuation of steroids in steroid-induced psychosis
  - Immunomodulatory therapy in Down syndrome regression with elevated anti-TPO Ig

Modifiers of underlying pathophysiological circuitry

- Psychiatric agents may have direct impact on illness state and may decrease likelihood of future illness
- Examples:
  - Lithium in idiopathic bipolar disorder
  - Methylphenidate in substance use disorder development in the setting of attention-deficit/hyperactivity disorder
  - Exposure with response prevention + SSRI in obsessive-compulsive disorder

Symptom modifying agents

- Instances where a treatment is more beneficial than simple sedation
- Examples
  - Most psychiatric treatment
    - Antidepressants in depression
    - Antipsychotics in schizophrenia
    - Alpha agonists for ADHD
  - Antipsychotic agents in agitation in ASD
  - Lorazepam in catatonia

Sedation

- Often used for acute management or aggression
- Examples
  - Hydroxyzine in anxiety
  - Clonidine for acute agitation
  - Trazodone for insomnia

Behavioral therapies

- Parent-focused therapies are the mainstays in behavioral disorders in children
  - Strong evidence-base for ODD, DMDD, etc.
  - Parent management training (PMT)
  - Parent/child interaction therapy (PCIT)
- Behavioral therapies such as ABA are commonly used in ASD
- Supportive, play, psychodynamic, exposure, acceptance and commitment therapies are all potentially appropriate modalities for various specific indications
- Speech therapy is often part of treatment for social/pragmatic deficits
- Occupational therapies are often utilized to aid behavioral difficulties, ASD, etc

Psychopharmacology in rare diseases

- Rarely studied
- Little evidence base
- Case-reports frequently utilized
- Idiosyncratic prescription patterns
- Off-label usage of medications

Specific drug recommendations

- Trazodone

SLEEP DISTURBANCE AND RAGE ATTACKS IN OPSOCLONUS-MYOCLONUS SYNDROME: RESPONSE TO TRAZODONE

MICHAEL R. PRANZATELLI, MD, ELIZABETH D. TATE, C-FNP, MN, WILLIAM S. DUKART, MD, MARY JO FLINT, MD, MICHAEL T. HOFFMAN, MD, AND AMY E. OKSA, MD

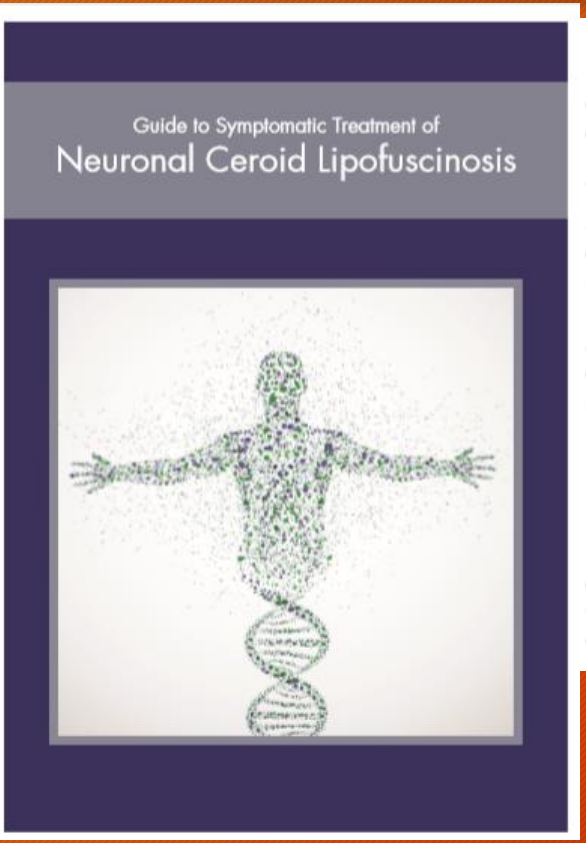
Objectives Parents of children with opsoclonus-myoclonus syndrome (OMS) frequently describe poor sleep and rage attacks. We hypothesized that these manifestations are related and could result from underlying monoaminergic dysfunction.

Study design We clinically characterized the sleep and behavioral characteristics of 51 young children with OMS; 19 of those with the most disruptive sleep patterns were treated with trazodone, a soporific serotonergic agent.

Results Sleep disturbances, including prolonged sleep latency, fragmented sleep, reduced quantity of sleep, snoring, and nonrestorative sleep, were reported in 32 children, and frequent rage attacks were reported in 25. In 59% of the poor sleepers, parents felt that the problem was severe enough to warrant treatment. Children sleeping <10 hours/night had a higher rage frequency than those who slept more. Of the children who required trazodone, 84% were receiving corticosteroids or adrenocorticotropic hormone (corticotrophin), compared with 37% in the subgroup with normal sleep. Trazodone (3.0 ± 0.4 mg/kg/day) improved sleep and behavior in 95% of the children, significantly increasing total sleep time by 72%, decreasing the number of awakenings by 76%, and reducing rage attacks by 33%.

Conclusions Children with OMS exhibited multiple types of sleep disturbances, which contributed to rage attacks. Trazodone was effective in improving sleep and decreasing rage attacks and was well tolerated, even in toddlers. *(J Pediatr 2005;147:372-8)*

Batten disease recommendations



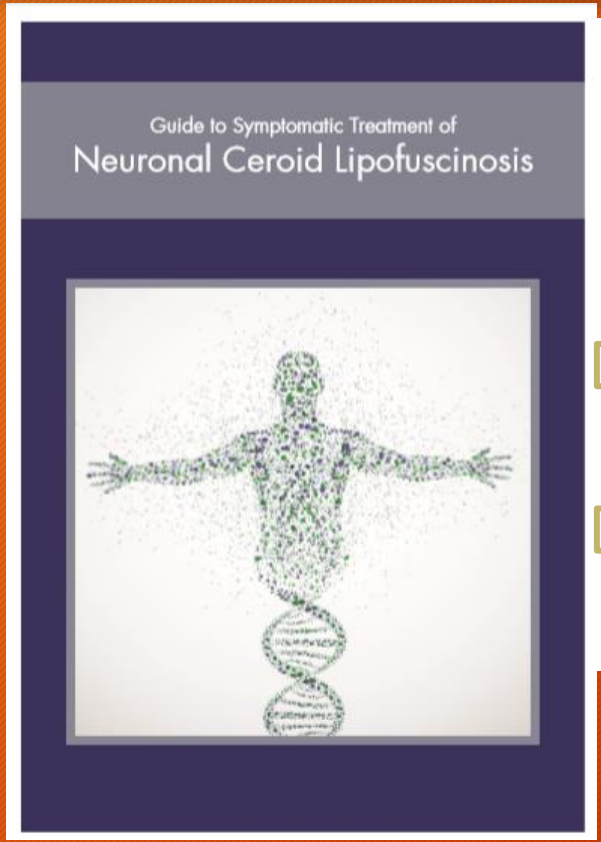
In order to help individuals with JNCL, it is important to assess and acknowledge the psychiatric symptoms, and to implement treatment where indicated. It may be relevant to evaluate all newly-diagnosed patients using standardized tools and to follow up on these evaluations regularly.

Treating the patient's symptoms can be challenging, both due to the considerable range of symptoms, and due to polypharmacy considerations (many patients are also taking anti-epileptic and anti-parkinson medication). It is therefore important to evaluate the patient's symptoms carefully to find the optimal treatment given his or her individual symptoms.

A study from Finland (Backman, Aberg, Aronen, & Santavuori, 2001) showed that citalopram (Citalopram®, Cipramil®) is effective against affective symptoms with few side-effects. Escitalopram (Cipralex®) has also been proven effective. Lamotrigine, which is used to treat epilepsy, also has a mood stabilizing effect. In our experience, sertraline hydrochloride (Zoloft®) is effective against depression.

Risperidone (Risperdal®, Rispolept®) has been used to treat psychosis with good results. Experiences with aripiprazole (Abilify®) are limited but good. It has been said to be effective against organic psychoses. The most common side-effects include fatigue during the initial phase, weight gain and extrapyramidal symptoms. Klonazepam (Rivotril®), which is registered as an anti-epileptic drug, may, in some cases, also be effective.

Batten disease recommendations



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Batten disease recommendations

- For example:
  - “Currently, all treatment for JNCL is symptomatic. Psychotic, affective, and schizophreniform features are managed with citalopram, risperidone, olanzapine, or quetiapine.” [Bozorg et al 2009]

- For example: [Ostergaard 2016]

Table 3

Medications most often used in epilepsy and behavioral impairment in patients with juvenile neuronal ceroid lipofuscinosis (JNCL)

Symptom	Medication	Special comments when used in patients with JNCL
Epilepsy	Valproate	Be aware of hyperammonemia and valproate-induced hyperammonemic encephalopathy. Supplementation with L-carnitine may reduce the risk.
	Levetiracetam	Severe agitation has been reported in JNCL patients.
	Lamotrigine	
	Clonazepam	May also have a positive effect of restlessness.
	Topiramate	Risk of agitation has been reported in JNCL patients.
Behavioral symptoms	Citalopram	Especially for depression and aggression.
	Risperidone	In cases of hallucinations, delusions, agitation, or restlessness.
		Be aware of possible extrapyramidal side effects.
		Do not exceed 2 mg/24 hours.

Batten disease recommendations

- Risperidone and citalopram [Backman et al 2001]
  - 14 Finnish patients
  - Past medication trials identified by parent interview, medications identified included olanzapine, citalopram, risperidone, quetiapine
  - Perhaps more about prescribing habits than the medications themselves

Example of evidence bases in neuropsychiatry

Neuropsychiatric syndrome	1st-line therapies*	2nd-line therapies	3rd-line therapies
Agitation in AD	Citalopram (10–30 mg/day)** Risperidone (0.5–1 mg/day)	Aripiprazole (10 mg/day) Carbamazepine (300 mg/day) Dextromethorphan/quinidine (20/10 mg BID) Olanzapine (5–10 mg/day) Quetiapine (200 mg/day) Trazodone (50–100 mg/day)	Lamotrigine (25–100 mg/day) THC (2.5–7 mg/day)
Apathy in AD	Methylphenidate (20 mg/day)	Modafinil (200 mg/day)	
Depression in AD	Citalopram (10–40 mg/day)** Escitalopram (5–20 mg) Sertraline (50–150 mg)	Aripiprazole as augmentation (2 mg–15 mg/day) Bupropion (100 mg–300 mg/day) Carbamazepine (augmentation) (300 mg/day) Duloxetine (20–60 mg/day) Fluoxetine (20–40 mg/day) Mirtazapine (7.5–30 mg/day) Paroxetine (10–40 mg/day) Quetiapine as augmentation (25–200 mg/day) Venlafaxine (37.5–225 mg/day)	Electroconvulsive therapy Tricyclic antidepressants
Depression in PD	Pramipexole (0.3–4.2 mg/day) Ropinirole (10 mg/day)	Citalopram (10–20 mg/day) Desipramine (25–75 mg/day)*** Nortriptyline (25–75 mg/day)*** Sertraline(25–50 mg/day)	Electroconvulsive therapy Buproprion (100–300 mg/day) Duloxetine (30–60 mg/day) Mirtazapine(30 mg/day) Paroxetine (10–40 mg/day) Venlafaxine (37.5–225 mg/day)
Psychosis in PD	Pimavanserin (40 mg/day)	Clozapine (6.25–50 mg/day) Quetiapine (25–100 mg/day)	Risperidone (0.5–2 mg/day) Olanzapine (5–7.5 mg/day)

*Initiation of pharmacological interventions should occur after non-pharmacological approaches, cognitive enhancers, and comprehensive assessment of medical and environmental factors has been completed

**Maximum recommended dose for citalopram in patients over the age of 60 is 20 mg/day

***TCA should not be used in patients with cognitive impairment

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	Non-medication interventions	Treatments		
		1st	2nd	3rd
Agitation/ aggression	PMT techniques, safety-proofing	Alpha-agonist SSRI/SNRI Beta blocker	SGA Mood stabilizer Nuedexta (PBA)	FGA Mood stabilizer
Psychosis	CBT for psychosis, environmental management	SGA	FGA	ECT Clozapine Mood stabilizer
Impulsivity	Safety-proofing, PMT techniques	Alpha agonist Bupropion SNRI	Stimulant Non-stimulant wakefulness med Amantadine	SGA/FGA Mood stabilizer
Self-injury	Behavioral techniques, safety interventions	Alpha-agonist Beta blocker SSRI/SNRI Mirtazapine	Naltrexone NAC Buspirone	SGA/FGA Mood stabilizer
Delirium	Environmental management, optimize sleep, preventative measures	Clonidine	Haloperidol Risperidone quetiapine	Dexmedetomidine
Social pragmatics deficits	Group-based therapies School-based social pragmatics structured groups	Limited evidence for multiple agents. Manage comorbidities: CBT, SSRIs, propranolol for anxiety Stimulants, alpha agonists for ADHD		

Treatment recommendations

- Aggressively manage sleep
  - Melatonin>clonidine>trazodone
- Early behavioral therapies and supports for parents where possible
- Closely attend to symptoms of trauma for patient and family
  - Psychotherapy>prazosin/clonidine>SSRI
- Low threshold for management of neuropsychiatric symptoms (whether direct or indirect effects of OMAS, or unrelated)
- Manage behavioral symptoms with least side-effect laden medications, with escalation where necessary
- Appropriate social and educational supports
- Serial neuropsychological/psychoeducational testing wherever possible
- Low threshold for more aggressive psychotherapeutic or psychopharmacological interventions for psychiatric symptoms as they develop, knowing OMAS patients may have multiple risk factors and may be more susceptible

Areas of potential research

- Behavioral phenotype data in OMAS
- Rates of neuropsychiatric symptoms
  - Defining the spectrum of problematic symptoms
  - Understanding rates of specific psychiatric comorbidities compared with same-age peers
  - Susceptibility to subsequent stressors
- Association between sleep fragmentation and other symptoms
  - Will improvements in sleep directly or indirectly improve rage
  - How to optimize sleep management with minimal risk/fewest agents
- What are clinician prescribing patterns for behavioral symptoms in OMAS and are they effective?
- What agents are used prior to antipsychotics?
- What is the relationship between OMAS flares and neurobehavioral symptoms?
- Managing transitions of care
- Early use of behavioral interventions (benefits/detriments)
  - PMT
  - PCIT

Questions?

- Thank you!