Dystonia – an overview

Silke Cresswell, MD
Movement Disorder Neurologist
Associate Professor
Marg Meikle Professorship for Parkinson's diseae
Djavad Mowafaghian Centre for Brain Health
Pacific Parkinson's Research Centre
University of British Columbia

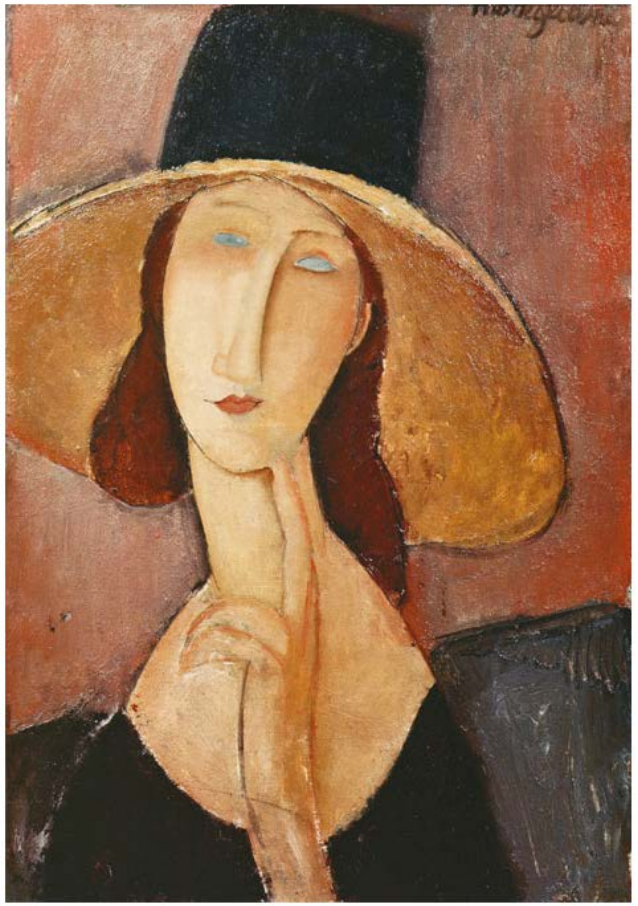
Disclosures

- Consulting for Ipsen, Allergan, Dysport
- Research support from Pacific Parkinson's Research Institute, Parkinson Canada, Parkinson's Society BC, Kurt Gagel gift, Mottershead Family gift, Canadian Institutes for Health Research, Weston Brain Institute, Canadian Consortium on Neurodegeneration and Aging
- Scientific Advisory Board Parkinson Canada, Dystonia Medical Research Foundation Canada
- Director National Canadian Movement Disorder Course for Residents

- I will discuss off-label medications

Overview

- What is dystonia?
- What are different forms of dystonia?
- What causes dystonia?
- What are treatment options for dystonia?



Cervical dystonia in Modigliani's "Jeanne Hebuterne in a Large Hat"? 1918

What is dystonia?

Twisted

- https://www.youtube.com/watch?v=qa5ybJoD_hc&feature=player_embedded

Dystonia

"Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.

Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation."

Albanese et al, consensus update on dystonia 2013,
Movement Disorder Society

Dystonia

- First described in the late 19th century
- Oppenheim introduced the term dystonia in 1911
- Dystonia can affect people of any age
- Dystonia as a symptom can be associated with a wide range of conditions, from mild to severe
- Dystonias are a fairly common form of movement disorders (300,000 people in Canada and US)
- Dystonias are chronic conditions

What are different forms of dystonia?

How to differentiate dystonia syndromes?

- At what age did it start?
- What body parts are affected?
- What was the onset like? How did it develop over time?
- Are there any other features associated with it?
- Cause:
  - Is it a condition running in the family or a genetically caused condition?
  - Are there changes in the brain or elsewhere in the nervous system?
  - Was there an outside event causing the dystonia such as a medication, a drug, an accident or an illness?

How to differentiate dystonia syndromes?

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This information helps to guide diagnosis and treatment

Categories of dystonia

- Primary dystonias
  - Dystonia (+/- tremor) is the only symptom of the condition
  - Genetic forms (e.g. DYT1)
  - Focal, “idiopathic” dystonia
- Secondary dystonias
  - Dystonia is caused by outside factor such as drugs, trauma, cerebral palsy, stroke, brain infection, brain tumor etc
- Dystonia plus
  - Dystonia is part of a variety of symptoms in a condition
  - E.g. Dopa-responsive dystonia, myoclonus dystonia
- Functional dystonias

Age of onset

- Infancy (birth to 2 years)
- Childhood (3–12 years)
- Adolescence (13–20 years)
- Early adulthood (21–40 years)
- Late adulthood (>40 years)

Are there differences between childhood and adult onset dystonias?

- Childhood onset:
  - More likely to start in the legs and spread to the trunk and rest of body ("generalize")
  - Focal dystonias are rare
  - More likely to be caused by a specific, identifiable underlying cause
  - Examples: cerebral palsy, genetic and metabolic causes

- Adult onset:
  - Focal dystonias more common (head/face/neck/arms)
  - Task-induced dystonias more common

Distribution of dystonia

- Focal:
  - one body region is affected
- Segmental:
  - two connected body regions are affected
- Multifocal:
  - non-connected body parts are affected
- Generalized
- Hemidystonia:
  - one side of the body is affected

Focal dystonias

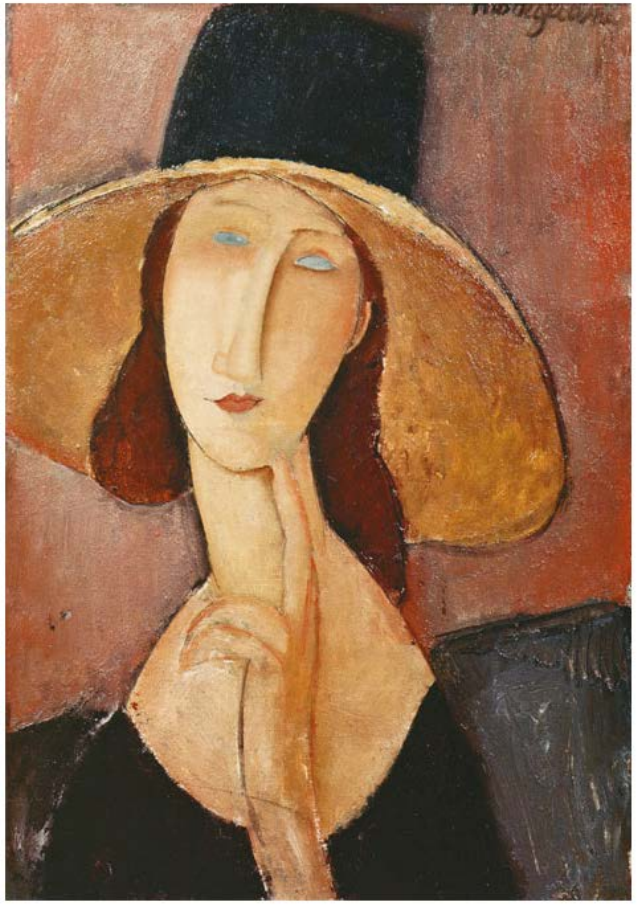
Eyelids	Blepharospasm
Mouth	Oromandibular dystonia
Larynx (voice box)	Laryngeal (voice) dystonia
Hand or arm	Writer’s cramp, limb dystonias

Sensory trick: Geste antagoniste

- Touching the affected body part might improve abnormal posturing
- At times, even thinking of touching might work

- Changing the type of pen used can improve symptoms of writer's cramp

- Changing sensory input



Focal task-specific dystonias

- Dystonia occurs only during specific tasks
- Tasks are usually performed repetitively
- Often affecting areas with high sensory input and fine motor output (e.g. finger, hand, mouth)

Focal task-specific dystonia

- Writing
- Sewing
- Telegraph machine
- Metal working
- Watch making
- Engraving
- Shoe making
- Runners
- Locksmithing
- Glass working
- Milkers
- Golfers
- Racquet sports
- Dart throwers
- Musicians

Genetic dystonias:
the example of DYT1 dystonia

- Oppenheim's torsion dystonia
- Young onset
- Isolated, generalized dystonia
- Occurs in all populations, more common in some populations (e.g. Ashkenazi Jewish)
- Gene: TOR1A, autosomal dominant, testing available
- 30% of gene carriers develop dystonia, if no dystonia by age 25 unlikely to develop symptoms
- Often responds to Deep Brain Stimulation

Overview of genetic dystonias

Locus	Disease	Type	Inh.	Gene name	Chrom.
DYT1	Oppenheim's torsion dystonia	ID	AD	*TorsinA*	9q34
DYT2	Early-onset recessive TD	ID	AR	*HPCL*	1p35
DYT3	Lubag (x-linked dystonia-parkinsonism)	CD	X-R	*TAF1*	Xq13.1
DYT4	Whispering dystonia (one family only)	ID	AD	*TUBB4*	–
DYT5a/b	Dopa-responsive dystonia	CD	AD	*GCH1*, *TH*, *SPR*	14q22.1
DYT6	Craniocervical dystonia (Mennonite/Amish)	ID	AD	*THAP1*	8q21-q22
DYT7	Familial torticollis	ID	AD	–	18p
DYT8	Paroxysmal non-kinesigenic choreoathetosis	ID/CD	AD	*MR1*	2q33-q35
DYT9	Paroxysmal dyskinesias with spasticity	CD	AD	*GLUT1* (*SLC2A1*)	1p21
DYT10	Paroxysmal kinesigenic dyskinesia	ID/CD	AD	*PRRT2*	16p11.2
DYT11	Myoclonus-dystonia	CD	AD	*e-SG*	7q21.3
DYT12	Rapid-onset dystonia-Parkinsonism	CD	AD	*ATP1A3*	19q13
DYT13	Craniocervico brachial	ID	AD	–	1p36
DYT15	Myoclonus-dystonia	CD	AD	–	18p11
DYT16	Dystonia-Parkinsonism	CD	AR	*PRKRA*	2q31.2
DYT17	Juvenile-onset TD with torticollis and dysarthria	CD	AR	–	20p11
DYT18	Paroxysmal exercise-induced dystonia	ID/CD	AD	*GLUT1* (*SLC2A1*)	1p31
DYT19	Paroxysmal kinesigenic dystonia 2	ID/CD	AD	–	16q13
DYT20	Paroxysmal non-kinesigenic dystonia 2	ID/CD	AD	–	2q31
DYT21	Pure dystonia, mixed distribution	ID	AD	–	2q14
DYT23	Cervical dystonia/myoclonus-dystonia	ID	AD	*CACNA1B*	9q34
DYT24	Mixed dystonia	ID	AD	*ANO3*	11p14
DYT25	Cervical dystonia	ID	AD	*GNAL*	18p11
DYT26	Myoclonic dystonia	CD	AD	*KCTD17*	22q12
DYT27	Cervical/limb/generalized	ID	AR	*COL6A3*	2q37
	Cervical dystonia	ID	AD	*CIZ1*	9q34

Inh., inheritance mode; Chrom., chromosomal region.

The assignment of a DYT number does not mean that the pathogenic role of mutations in the listed genes is unequivocally confirmed.

Verbeek, Gasser 2017

Dopa-responsive dystonia

- https://www.youtube.com/watch?v=jxFO-SjA-P4

Dopa responsive dystonia (DYT 5): typical presentation

- Childhood onset
- “Diurnal variation”: dystonia worse in evening
- Often onset in feet
- Mild parkinsonism
- Exquisite L-dopa responsiveness

Dopa responsive dystonia: typical presentation

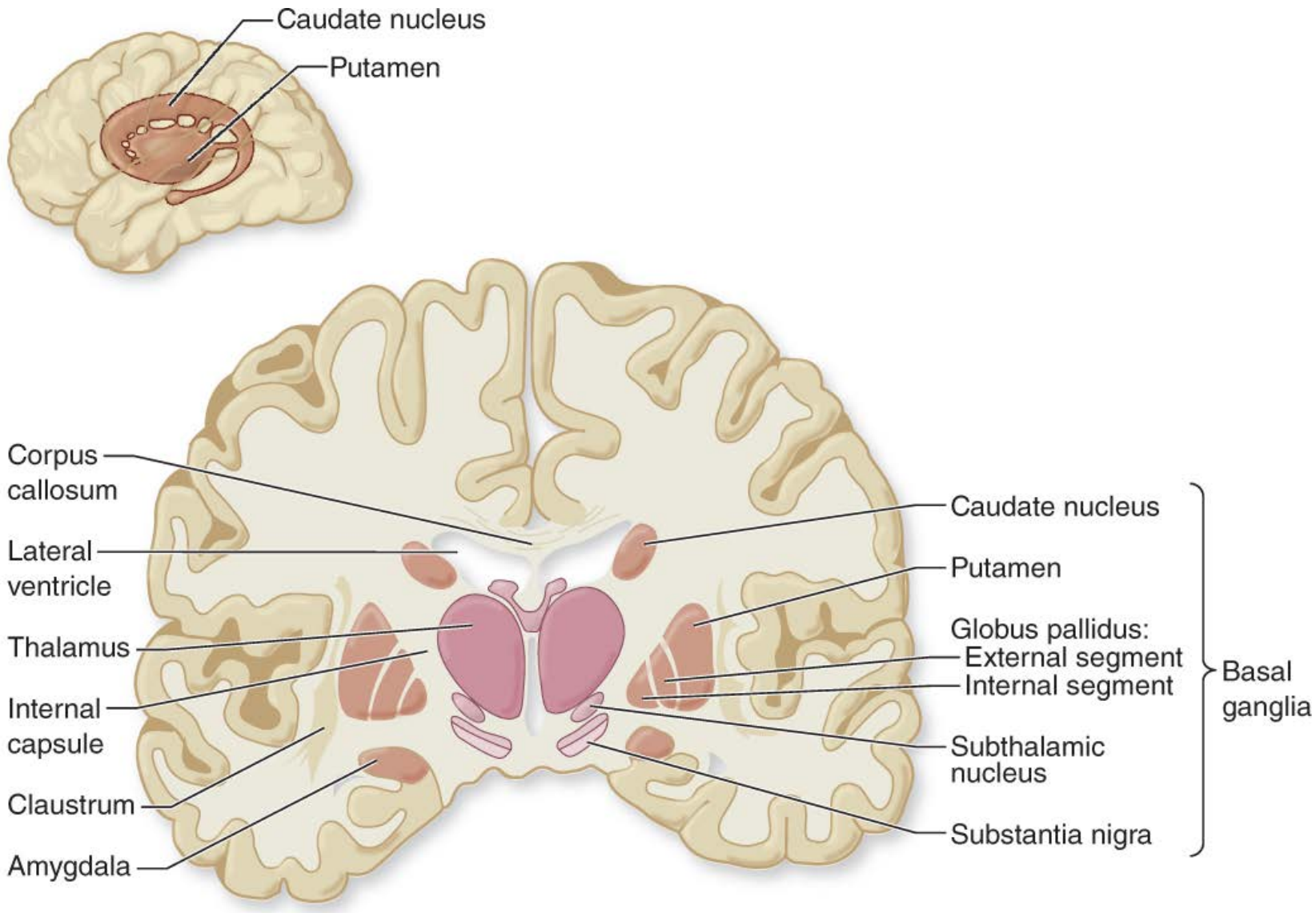
- Childhood ons
- Diurnal v
- Often
- Mild
- Exqu

Trial of levodopa in young patients with dystonia

What causes dystonia?

What causes dystonia?

- Exact cause not known
- Basal ganglia, sensorimotor networks and cerebellum/thalamus involved



Source: Ropper AH, Samuels MA, Klein JP: *Adams and Victor's Principles of Neurology, Tenth Edition:* www.accessmedicine.com

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What happens in the brain?

- Sensorimotor plasticity altered
- Lack of spatial specificity and reduced surround inhibition:
  - activating patterns not specific for one movement but at same time activating other movements that should be inactive
- Reduced inhibition of central nervous system on several levels (cortex, brainstem, spinal cord, cerebellum)

What does the work-up for dystonia look like?

- A classic presentation of a focal dystonia at the expected age might not need any work up beyond a clinical neurological assessment
- Depending on presentation, age, other symptoms etc:
  - blood work and urine copper analysis
  - MRI brain/spinal cord
  - Genetic analysis
  - Cerebrospinal fluid analysis
  - Levodopa trial
  - Electromyography

What are treatment options for dystonia?

Treatment options

- Medications
  - Oral: baclofen, benzodiazepines, anti-cholinergics (benzhexol, trihexyphenidyl), levodopa, tetrabenazine
  - Injections: botulinum toxin
  - Baclofen pump
- Surgery
  - Deep Brain Stimulation
  - (Lesioning surgery)
- Other methods
  - Retraining
  - Physiotherapy

Oral medications (and main side-effects)

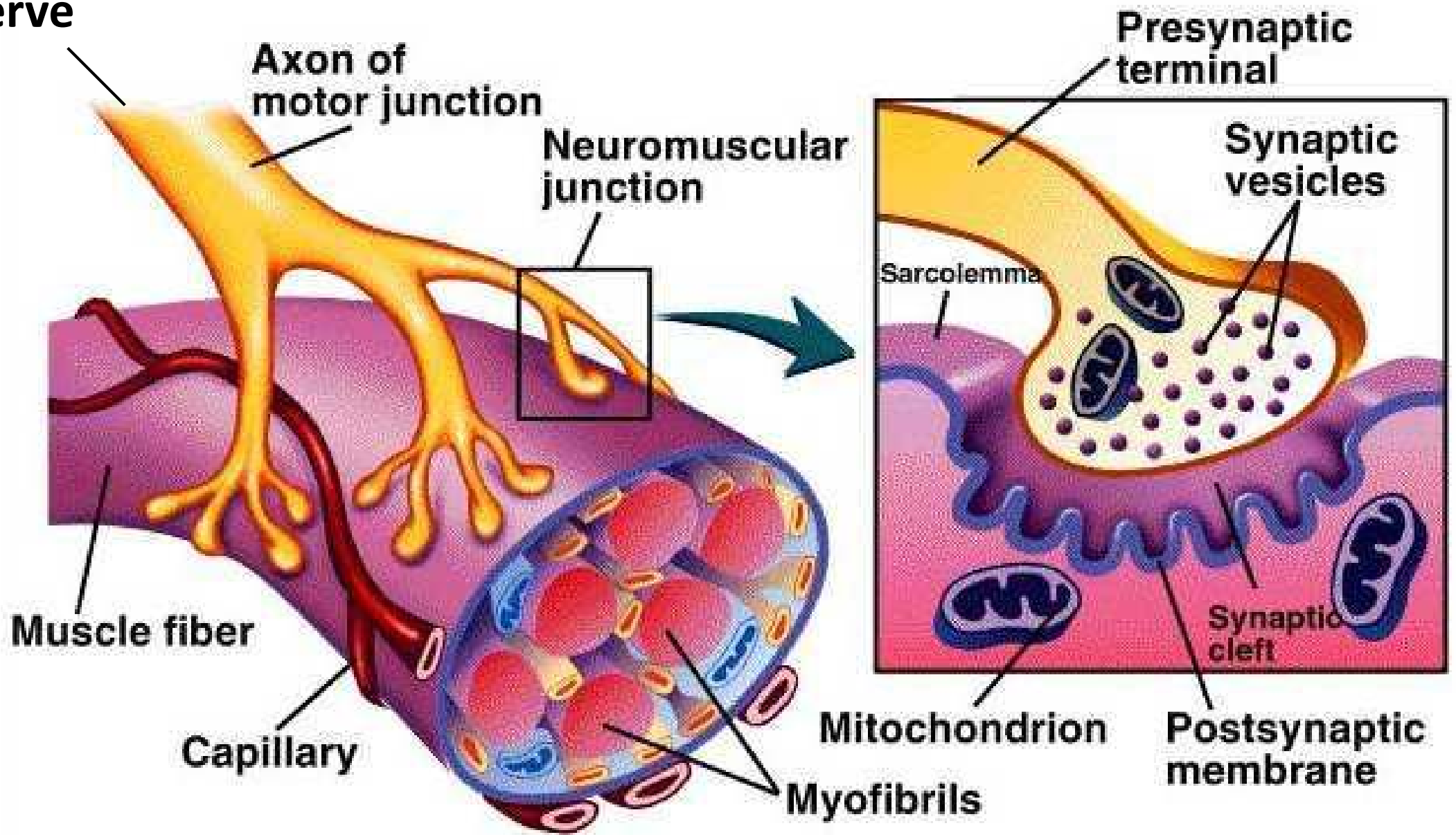
- anti-cholinergics (benzhexol, trihexyphenidyl)
  - Cognitive side effects, dry eyes/mouth, constipation, bladder problems
- Baclofen:
  - sedation
- Benzodiazepines
  - sedation, dependence
- levodopa
  - Nausea, low blood pressure on standing
- Tetrabenazine
  - Depression, sedation, parkinsonism

Mostly used in generalized dystonias

Focal dystonias: botulinum toxin injections

- First line treatment for focal dystonias
- 3 different botulinum toxin type A in Canada
- Toxin is produced by bacteria (clostridium botulinum)
- Botulinum toxins work locally at the muscle (neuromuscular junction)
- Interrupting communication between nerve and muscle so that muscle does not get command to contract (“chemo-denervation”)

Neuromuscular Junction

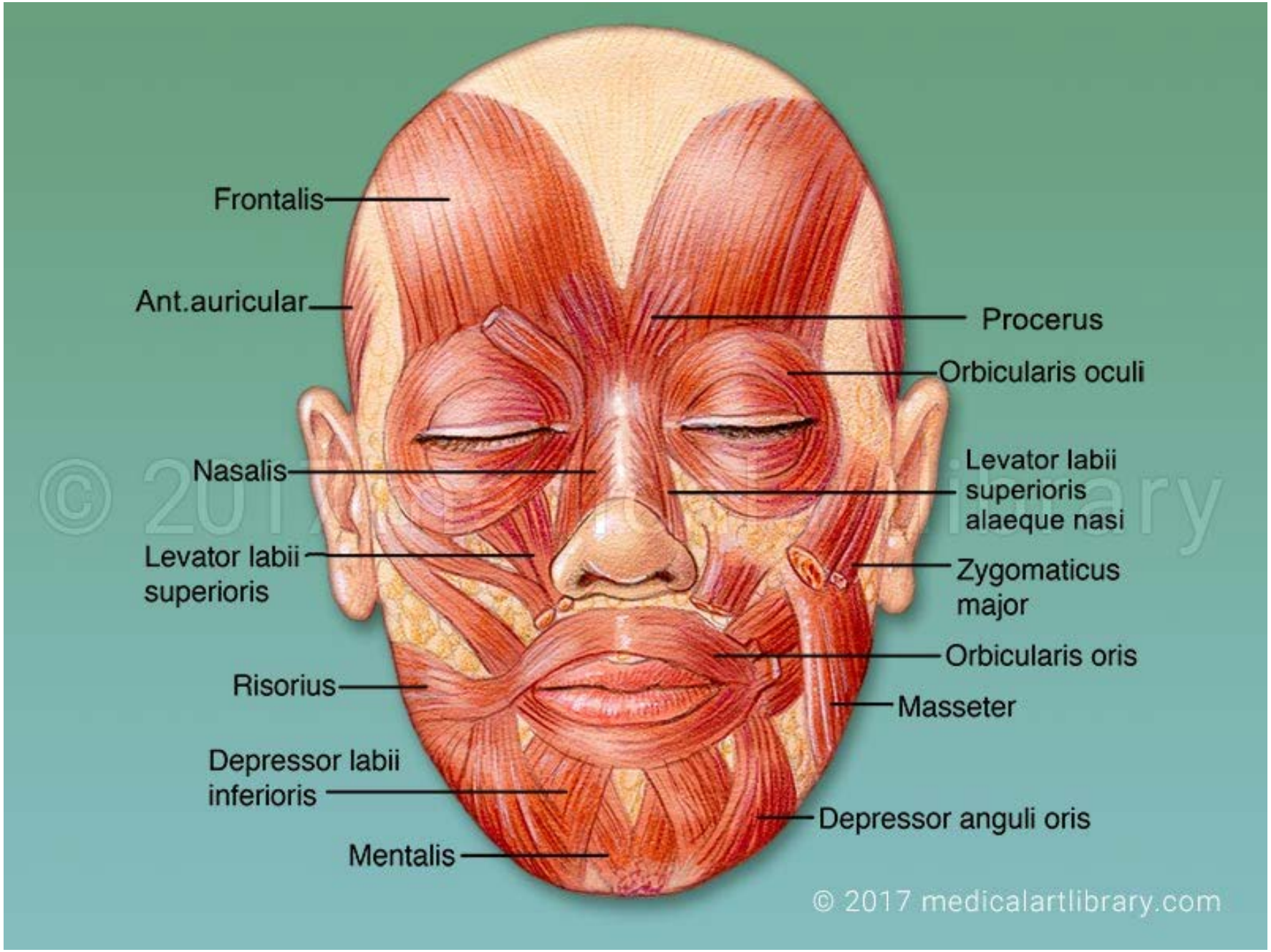


What are potential side-effects of botulinum toxin injections?

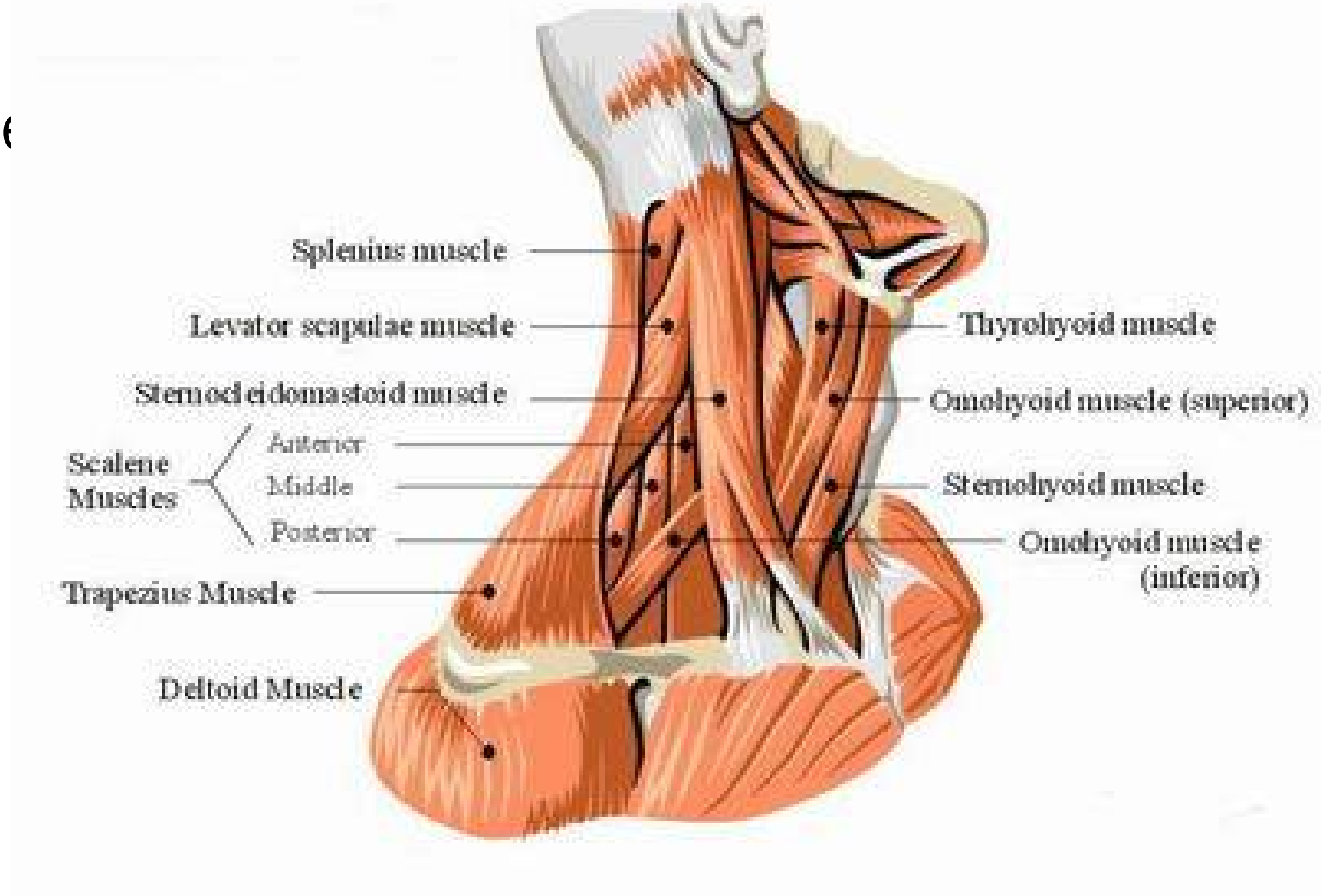
- Dosing ideally aims to reduce overactive muscle activity while preserving normal muscle activity
- Toxins usually take 1-2 weeks before becoming effective
- Wearing off after 8-16 weeks
- Main potential side effects:
  - Weakness of injected and neighbouring muscles
  - Swallowing difficulties (neck, jaw injections)
  - Dry mouth
  - Double vision, droopy eyelid (eye lid injections

  Depending on site of injection

Facial muscles



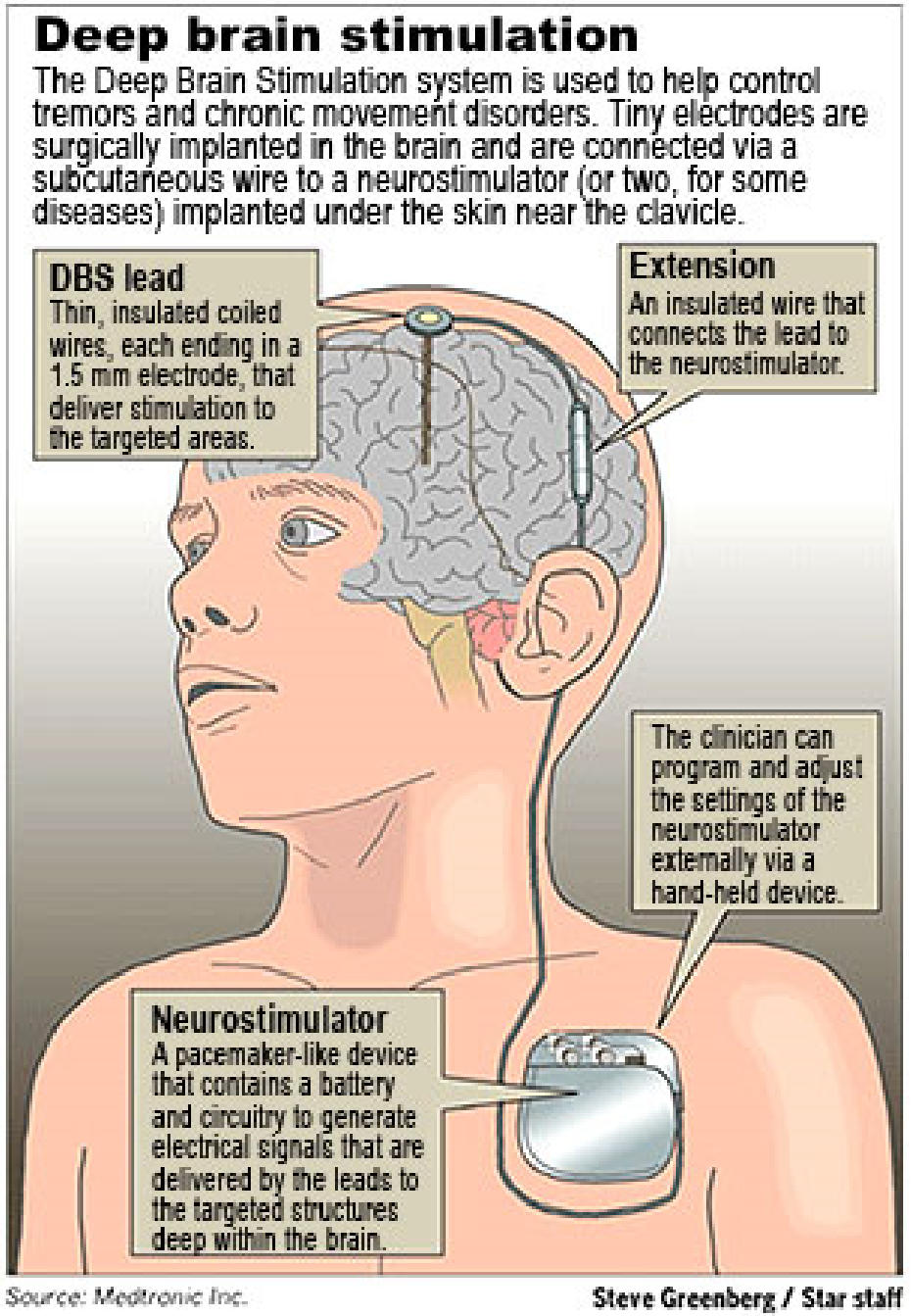
Neck muscle


Splenius muscle
Levator scapulae muscle
Sternocleidomastoid muscle
Scalene Muscles
Anterior
Middle
Posterior
Trapezius Muscle
Deltoid Muscle
Thyrohyoid muscle
Omohyoid muscle (superior)
Sternohyoid muscle
Omohyoid muscle (inferior)

Surgery

- Mainly Globus pallidus internus Deep Brain Stimulation (DBS) for primary dystonias (lesioning surgery in past)
- Full benefit after months
- Requires adjustments of stimulator settings
- Reversible, adjustable
- Potential problems: hardware, battery failure, infection, stroke, bleed
- Most successful for children with DYT1
- Medically refractory cervical dystonia, myoclonus dystonia, X-linked dystonia parkinsonism
- Less successful for secondary dystonias, although can be useful for some, e.g. tardive dystonias

Surgery


Deep brain stimulation
The Deep Brain Stimulation system is used to help control tremors and chronic movement disorders. Tiny electrodes are surgically implanted in the brain and are connected via a subcutaneous wire to a neurostimulator (or two, for some diseases) implanted under the skin near the clavicle.
DBS lead
Thin, insulated coiled wires, each ending in a 1.5 mm electrode, that deliver stimulation to the targeted areas.
Extension
An insulated wire that connects the lead to the neurostimulator.
The clinician can program and adjust the settings of the neurostimulator externally via a hand-held device.
Neurostimulator
A pacemaker-like device that contains a battery and circuitry to generate electrical signals that are delivered by the leads to the targeted structures deep within the brain.
Source: Medtronic Inc.
Steve Greenberg / Star staff

Physiotherapy and other strategies

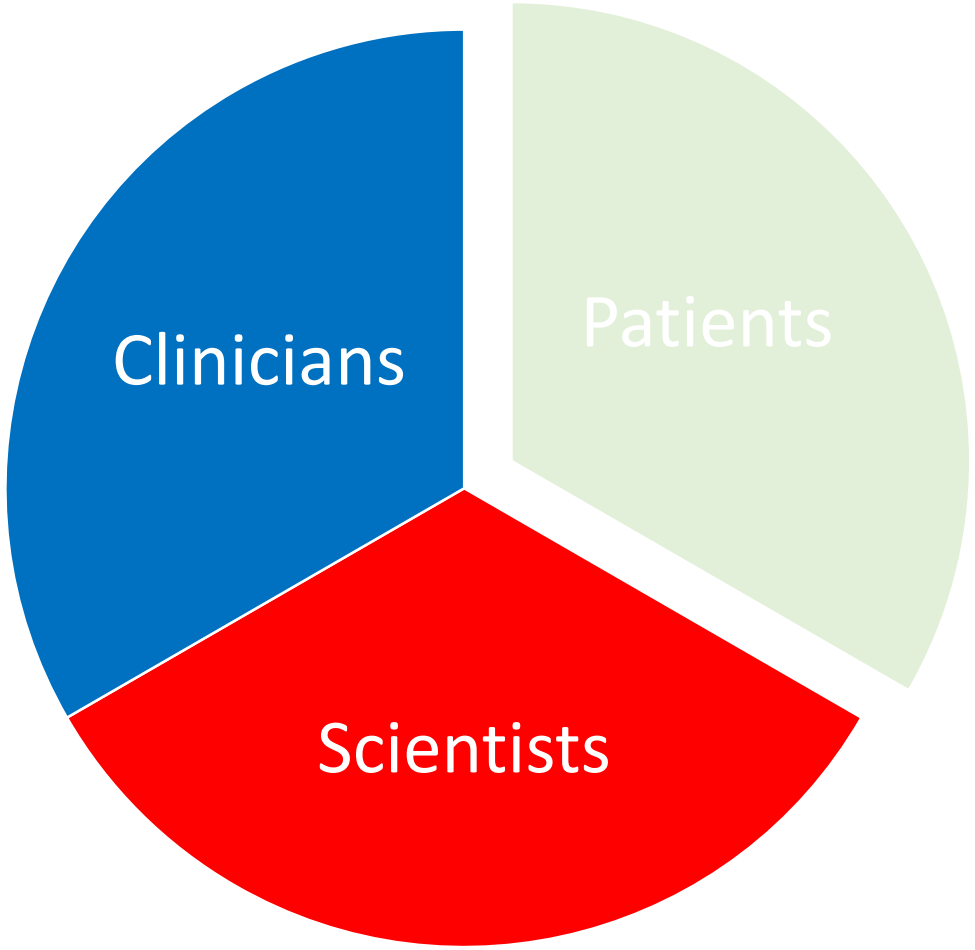
- Retraining therapies not generally clinically available but rather on research basis
- Physiotherapy: EMG biofeedback, muscular elongation, postural exercises, electrotherapy
- Physiotherapy: requires more studies, current studies with small numbers, using different methods and a variety of outcomes

- Increased anxiety and depression in primary dystonias
- Addressing anxiety, e.g. relaxation techniques, cognitive behavioural therapy
- Exercise is crucial for healthy living!

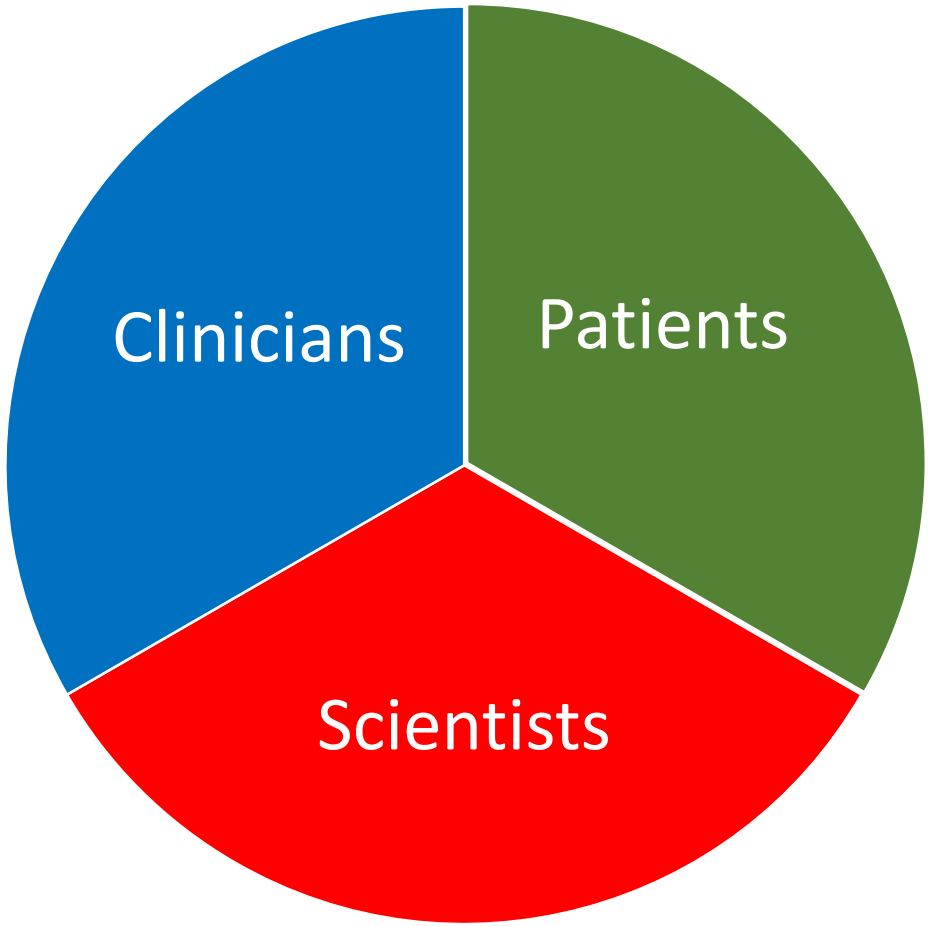
Conclusion

- Dystonias are quite common movement disorders
- Dystonias are associated with a wide variety of different conditions
- They can occur at any age
- Treatments mainly include botulinum toxin injections for focal dystonias, oral medications and surgery mostly for generalized conditions
- Physiotherapy, retraining and other therapies need more studies
- You are not alone!

Djavad Mowafaghian Centre for Brain Health – working *for* patients



Djavad Mowafaghian Centre for Brain Health – working *with* patients/clients

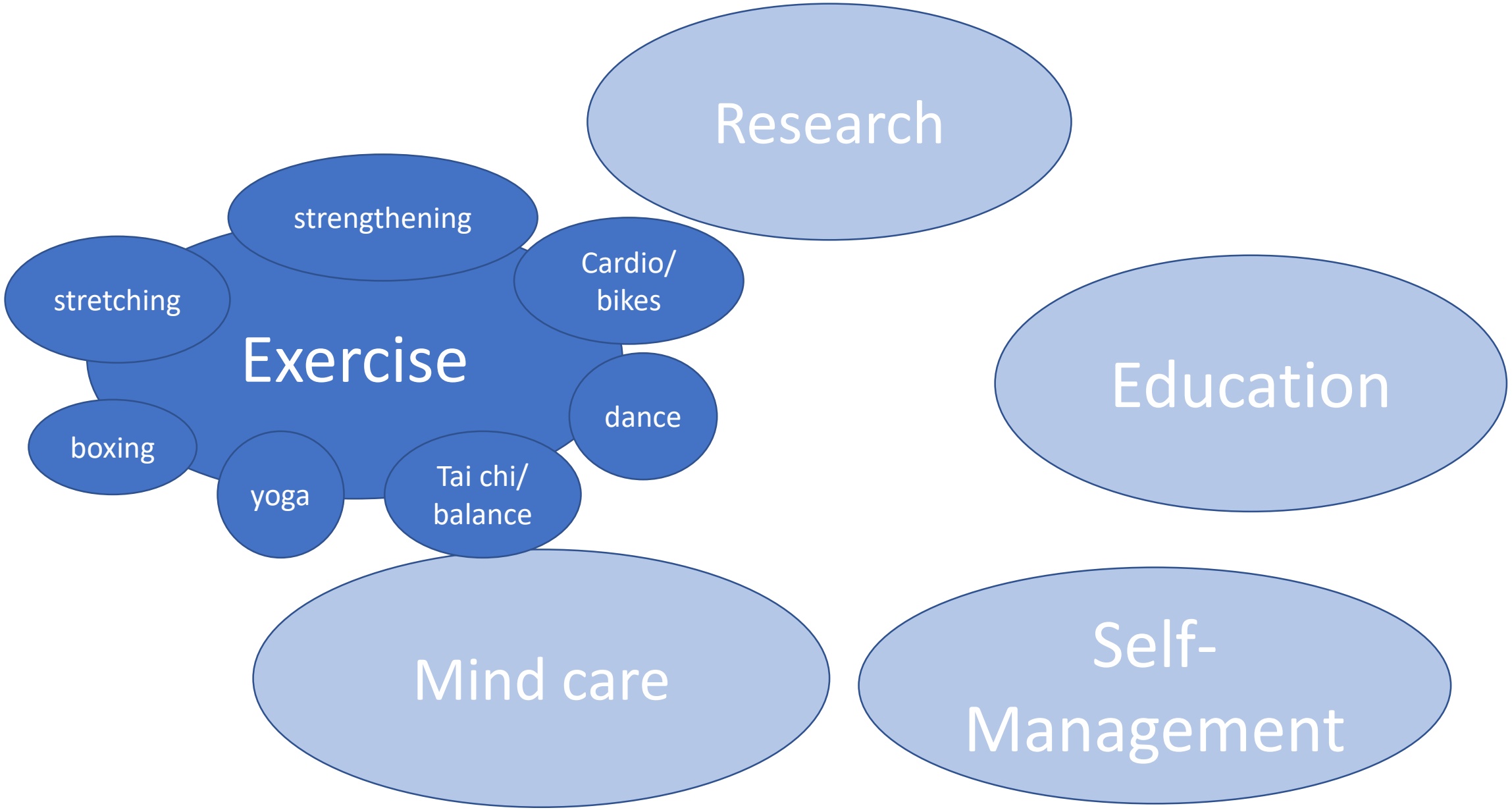


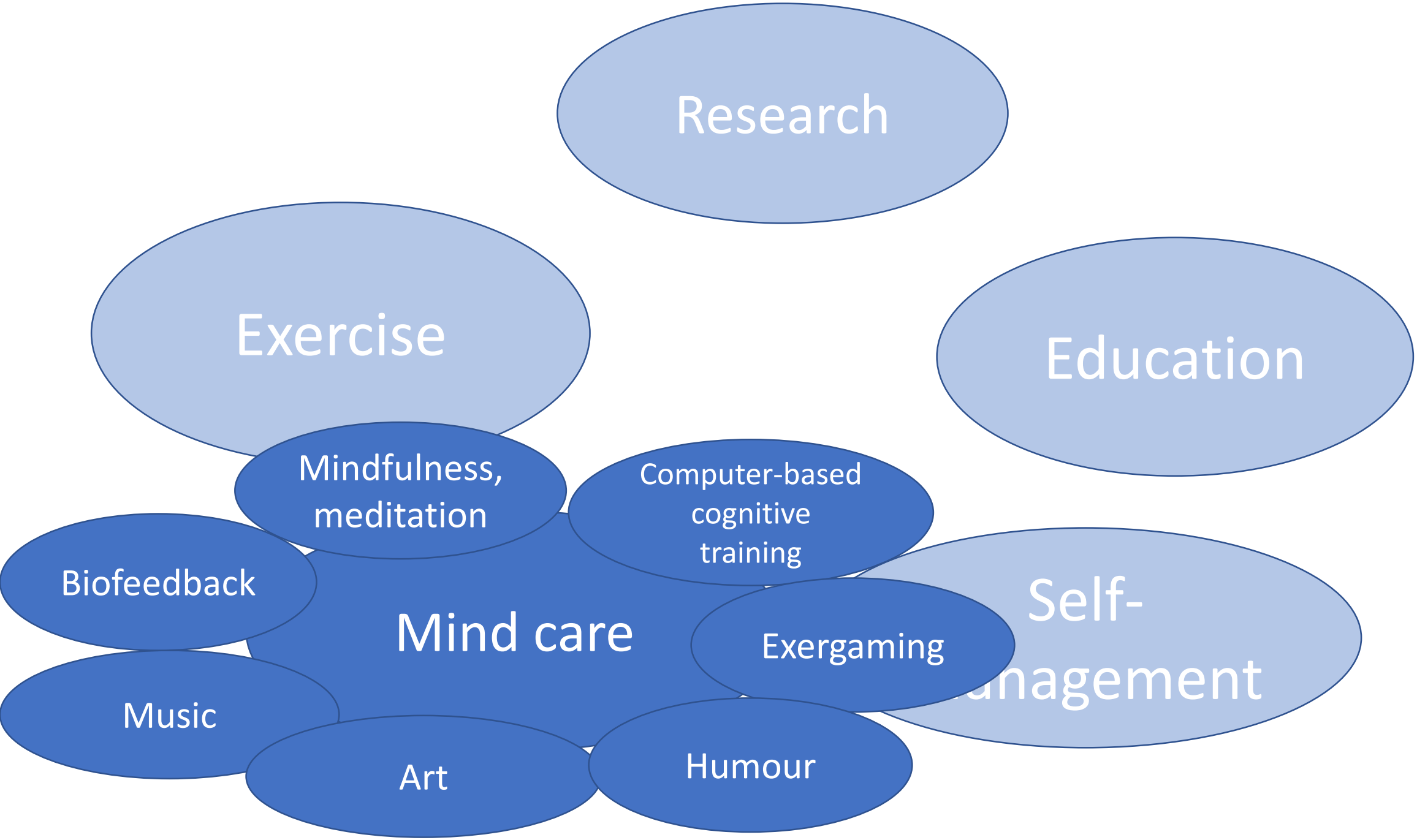
Foster Brain Health and active engagement in care and research

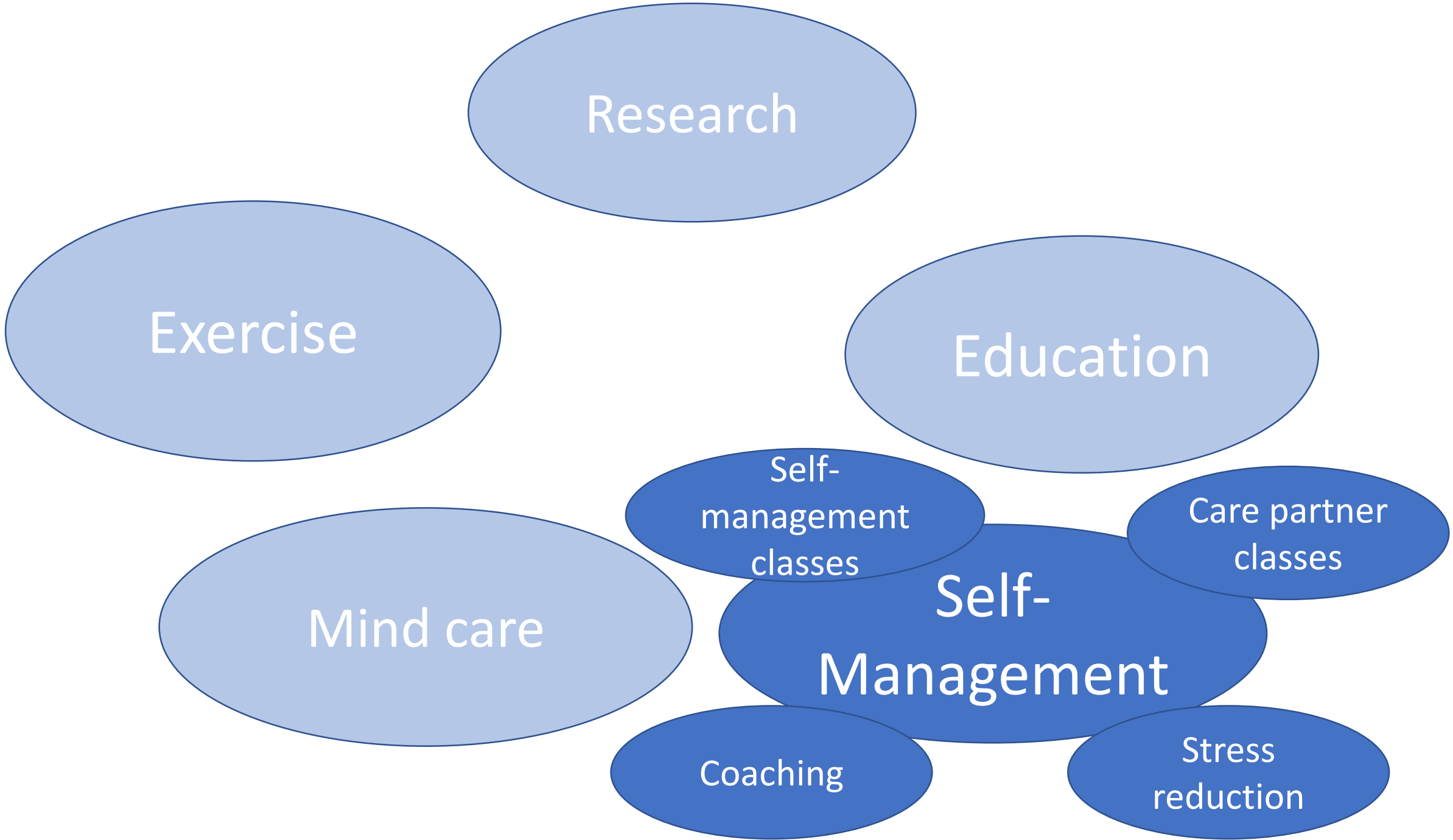
Brain Health and Wellness Program

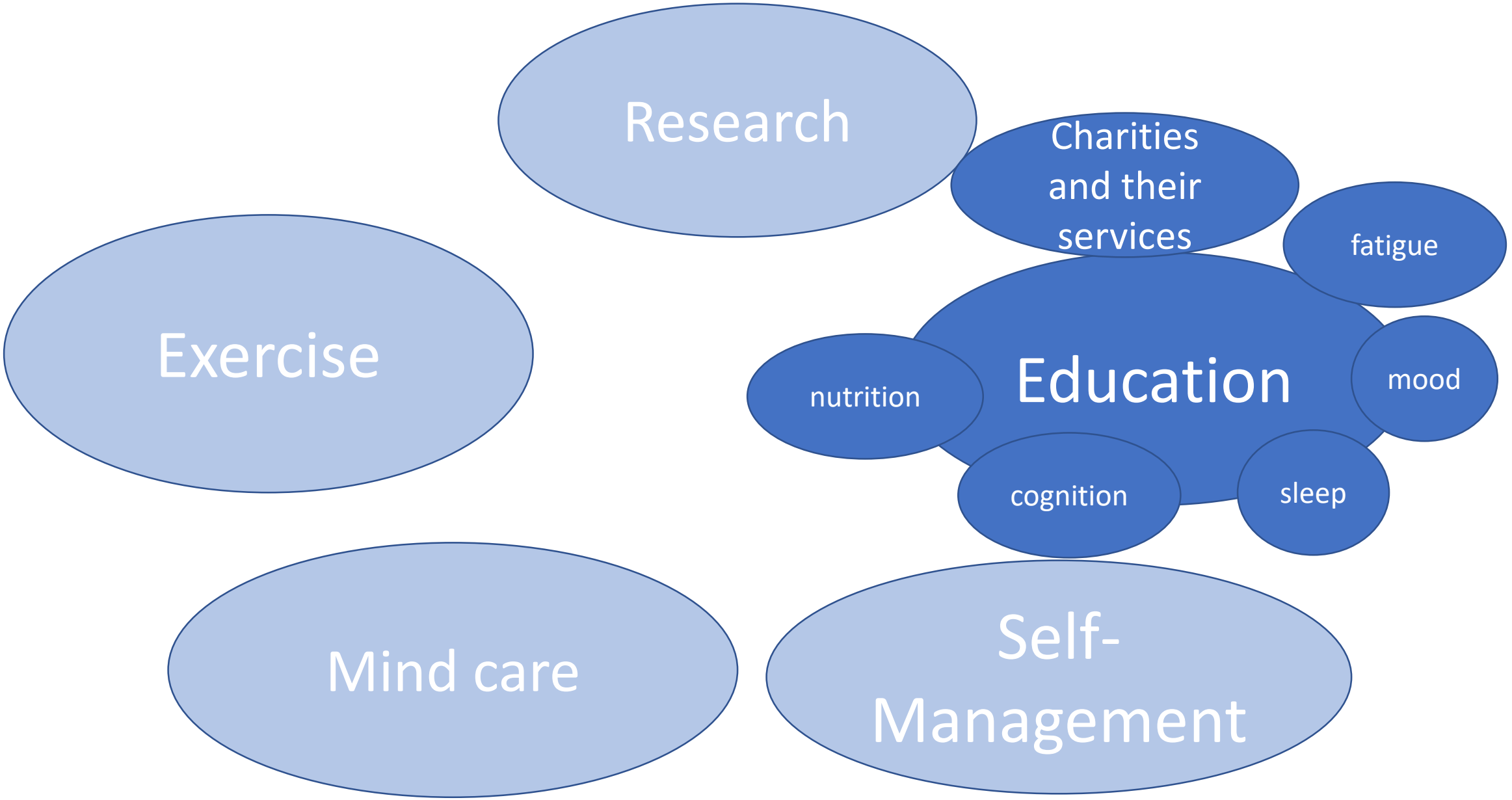
- Brain Wellness Program at CBH, serving people living with chronic brain disorders in the community
- Parkinson’s, dystonia and other movement disorders, Alzheimer’s, ALS, MS, Huntington’s, headache, mood disorders, traumatic brain injury, functional movement disorders, small vessel disease etc.
- Include care partners
- Similar to Heart Health, Cancer Gym programs
- Interdisciplinary program

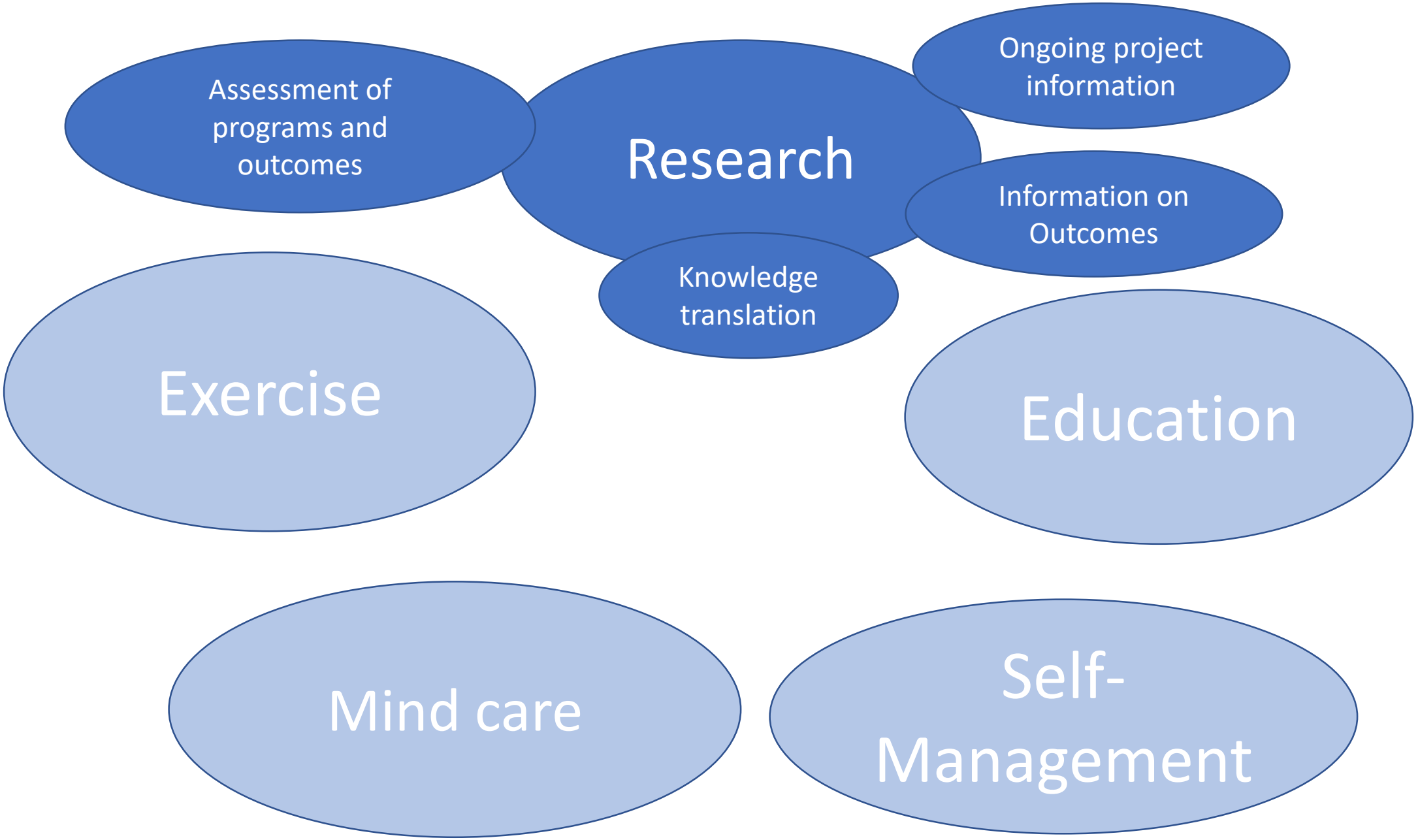

Research
Exercise
Education
Mind care
Self-
Management


Research
strengthening
stretching
Cardio/
bikes
Exercise
dance
boxing
yoga
Tai chi/
balance
Education
Mind care
Self-
Management


Research
Exercise
Education
Mindfulness, meditation
Computer-based cognitive training
Biofeedback
Mind care
Exergaming
Self-management
Music
Art
Humour


Research
Exercise
Education
Self-management classes
Care partner classes
Mind care
Self-Management
Coaching
Stress reduction


Research
Charities and their services
fatigue
Exercise
Education
nutrition
mood
cognition
sleep
Mind care
Self-Management


Assessment of programs and outcomes
Research
Ongoing project information
Information on Outcomes
Knowledge translation
Exercise
Education
Mind care
Self-Management

Thank you! Questions?

Djavad Mowafaghian Centre for Brain Health, UBC, Vancouver