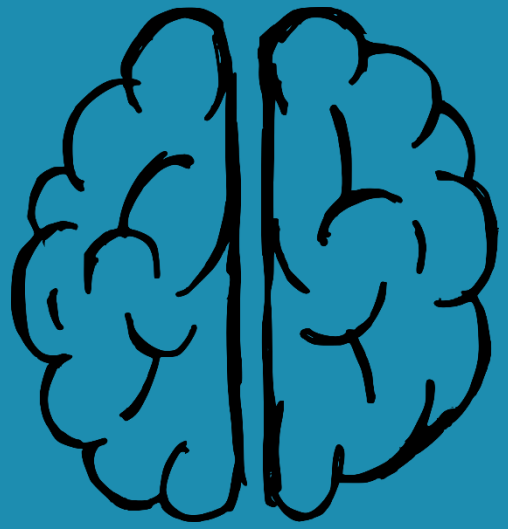
KU LEUVEN

PARENT

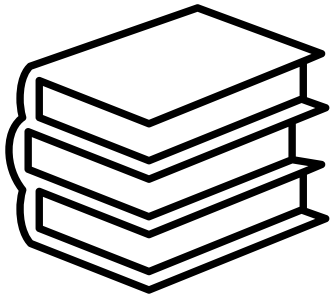
NEUROLOGICAL FACTORS DETERMINING VISUAL DEFICITS AND VISUOMOTOR CONTROL IN CHILDREN WITH UNILATERAL CEREBRAL PALSY



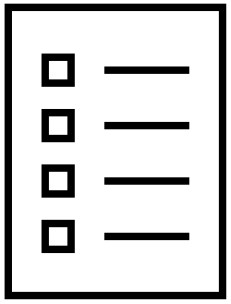
PhD Student: Monica Crotti
Supervisors: Els Ortibus
Co-supervisors: Hilde Feys and Lisa Mailleux
Mentor: Nofar Ben Itzhak

Locomotor and Neurological Disorders Group
Department of Development and Regeneration
KU Leuven, Belgium

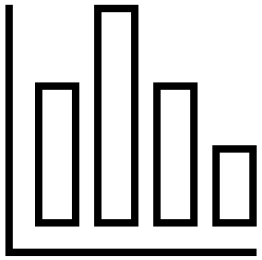
CONTENT



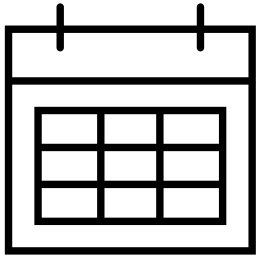
Background



Project



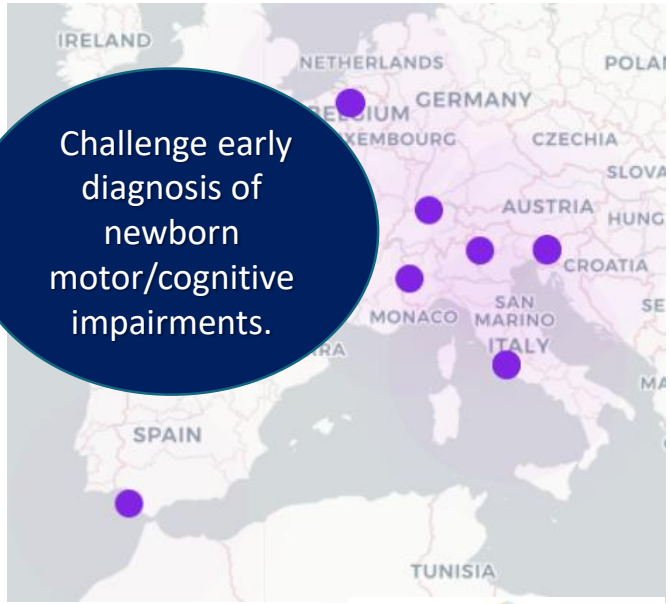
Analysis



Future steps

ITN **PARENT** Project

PremAtuRe nEwborn motor and cogNitive impairmenTs: Early diagnosis



Innovative training context
for **15 Early Stage Researchers**

Supervisor

Els Ortibus
MD, PhD

Co-Supervisors

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PT, PhD

Lisa Mailleux
PT, PhD

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Msc, PhD

PhD Researcher

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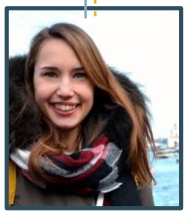
Grant Agreement N° 956394

FWO Project

Supervisors And Co-supervisors

PhD Researchers



Monica Crotti

PARENT

Lisa Decraene
FWO project

fwo

Lize Kleeren

Departmental financing

KU LEUVEN

Focus of the PhD

- **Visual deficits**
- **Visuomotor and bimanual motor control**

- **Bimanual motor control**
- **Mirror movements**

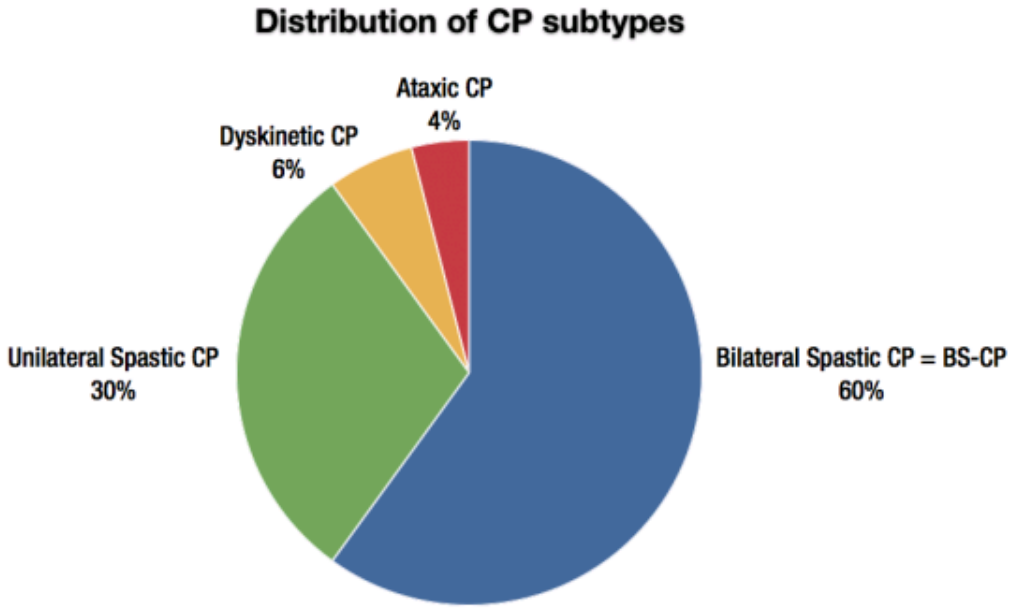
- **Proprioception**
- **Somatosensory**
- **Training program**

What is Cerebral Palsy?

- Permanent, non-progressive disorder
- Due to **brain damage [=cerebral]**
- It is the most common cause of childhood motor disability

Different motor types **[=palsy]**

- **ATAXIC (4%)**
- **DYSKENETIC (6%)**
- **SPASTIC**
  - **Unilateral (30%)**
  - **Bilateral (60%)**



https://eu-rd-platform.jrc.ec.europa.eu/scpe_en

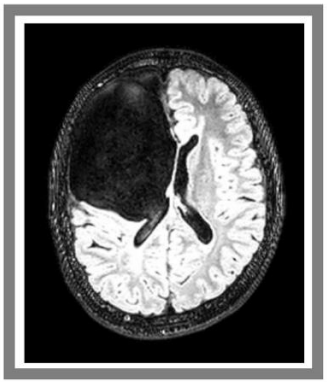
CP pathogenesis

MALFORMATION
Basic neural architecture damage

PERIVENTRICULAR LESION
Damage to the white matter tracts

CORTICAL – SUBCORTICAL
Grey matter damage

CORTICAL – SUBCORTICAL
Grey matter damage



Maldevelopments

Periventricular white matter lesions

Cortical and deep grey matter lesions

Cortical and deep grey matter lesions

1st and 2nd trimester | Early 3rd trimester | Late 3rd trimester

PREGNANCY

> 28 days postnatally
< 2-3 years of life

CONGENITAL CP

ACQUIRED CP

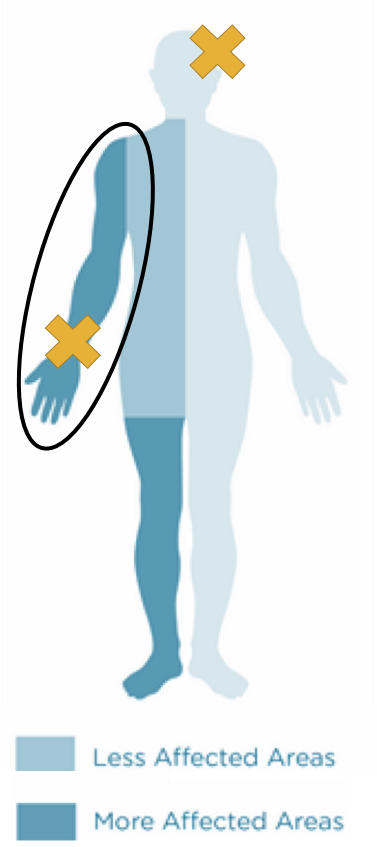
https://eu-rd-platform.jrc.ec.europa.eu/scpe_en

Unilateral Spastic Cerebral Palsy - uCP

- It accounts for **30%** of all cases
- Majority of studies focused on motor task

Unimanual motor tasks
→irregular movement of the **impaired arm**

Bimanual motor control
→ impaired movements when both arms/hands need to be coordinated



Hung et al. (2004); van Thiel et al.(2000); Mackey et al. (2006); Ronnqvist & Rosblad (2007); Chang et al. (2005)

Comorbidities in uCP

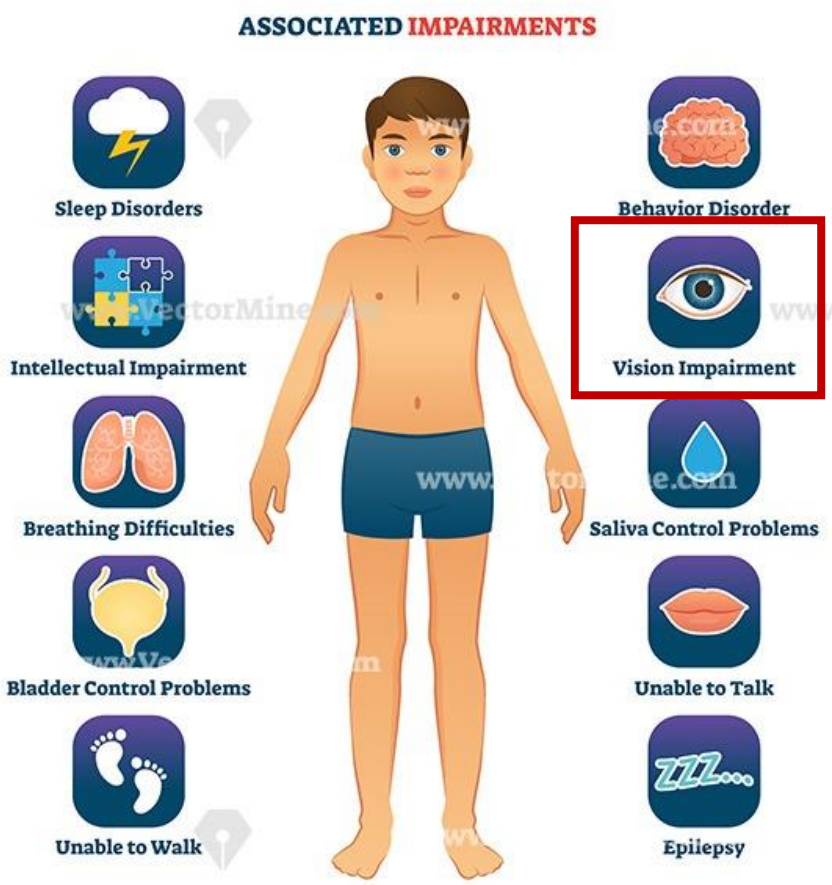
- **Visual comorbidities**
- 50% visual impairment
- 11% severe visual difficulties

Galli et al. (2008), Fazzi et al. (2012)

- Vision is **crucial** in planning movements
- Vision affects **everyday life activity**
- **Eye movements** support accurate hand movements

de Brouwer et al. (2021)

Lack of research on how visual deficits impact on bimanual functions in uCP



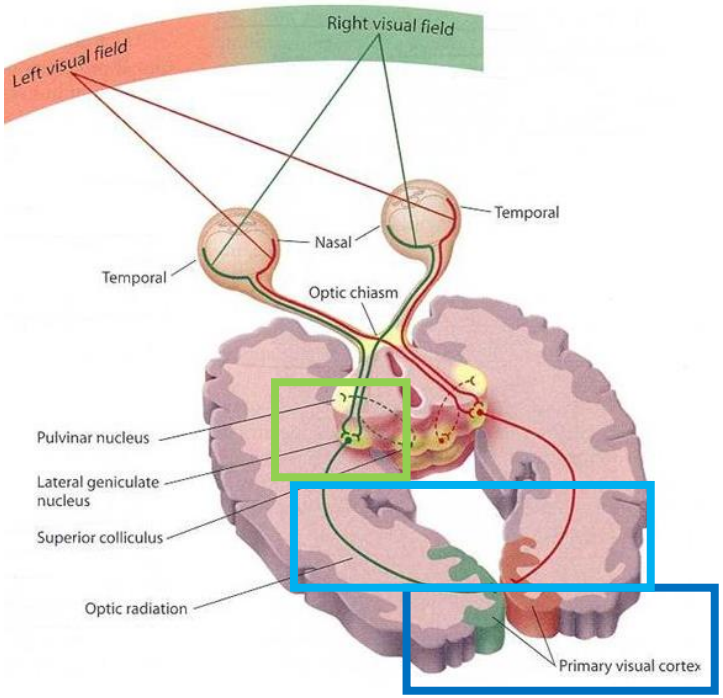
https://healthlibrary.askapollo.com/is-cerebral-palsy-reversible-know-the-facts/

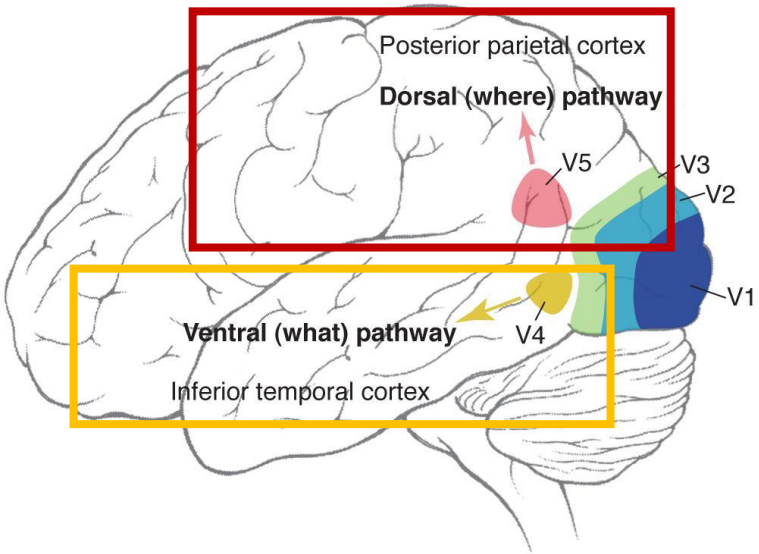
Visual system

a. Primary cortex (V1)

b. Extrastriate pathways

- Dorsal stream
  - parietal lobe
  - spatial and motion information
- Ventral stream
  - temporal lobe
  - recognizing shapes and objects





c. Midbrain structures

- Superior colliculus → to control eye movements
- Pulvinar → information transmission to and from the cortex

https://www.online-sciences.com/medecine/visual-pathway-functions-of-neurons-in-primary-visual-cortex-analysis-of-visual-information/

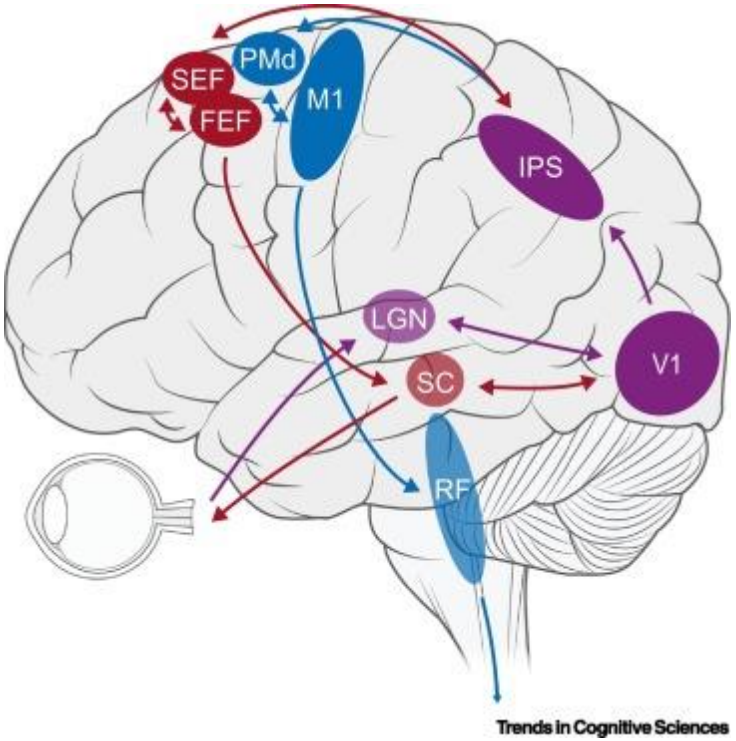
Vision and motor control in the brain

- **Occipital cortex** → visual information
- **Parietal and frontal cortices** → to transform visual information into a motor plan
- **Brainstem** → to the eye muscles and spinal cord for movement execution

Eye –hand interactions

1. **Posterior parietal cortex**

2. **Superior colliculus** (SC)
→ target selection for action

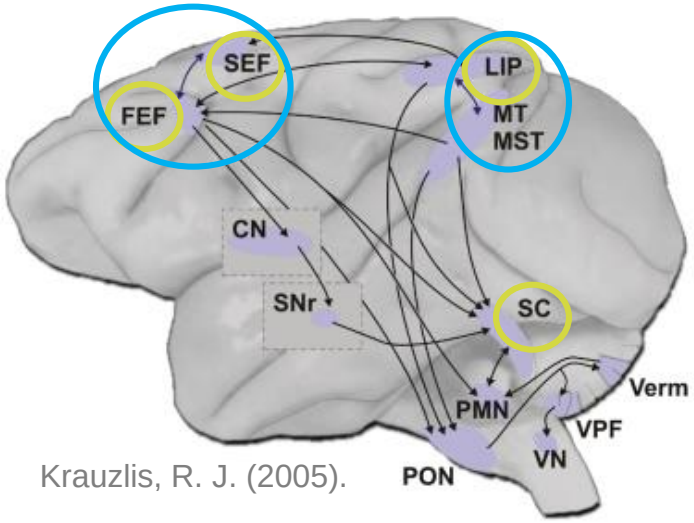


de Brouwer et al. (2021)

Eye movements

Saccades

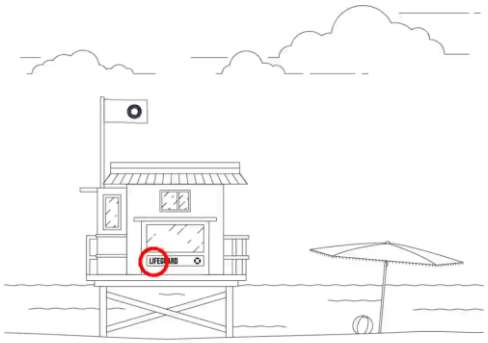
- rapid
- stationary targets
- voluntary or involuntary (reflex)
- no corrections



Krauzlis, R. J. (2005).

Smooth pursuit

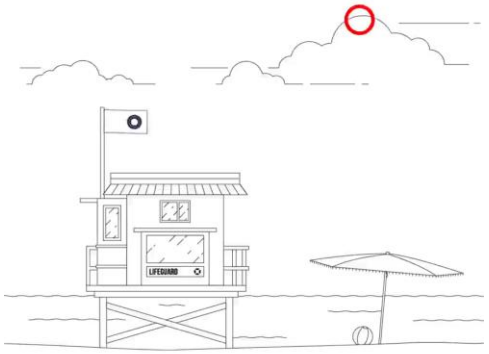
- slower
- moving stimulus on the fovea
- voluntary control
- corrected by visual feedback



de Brouwer et al. (2021)

Fixations

- Stops scanning of the scene
- Brain information processing

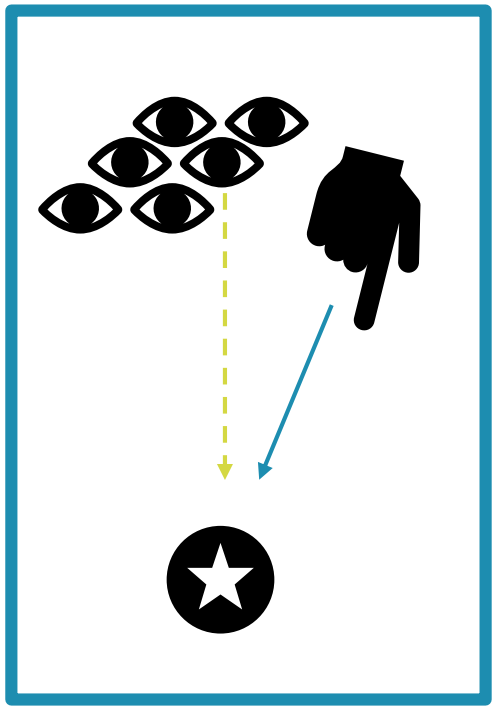


https://pupil-labs.com/blog/news/what-is-eye-tracking/

Vision and motor control – terminology

Eye movements

- ***Anticipatory Gaze Time***: Time between appearance of a starting stimulus and first gaze at the stimulus
- ***Movement Onset Asynchrony*** **(MOA)**: Time between the first gaze to the starting stimulus and hand initiation
- ***Frequency of gaze shift:*** Number of times the gaze moved in each sequence of movement



Action execution

- ***Movement time*** **(MT):** Time to complete each movement sequence

Saavedra et al. (2009)

Vision and motor control

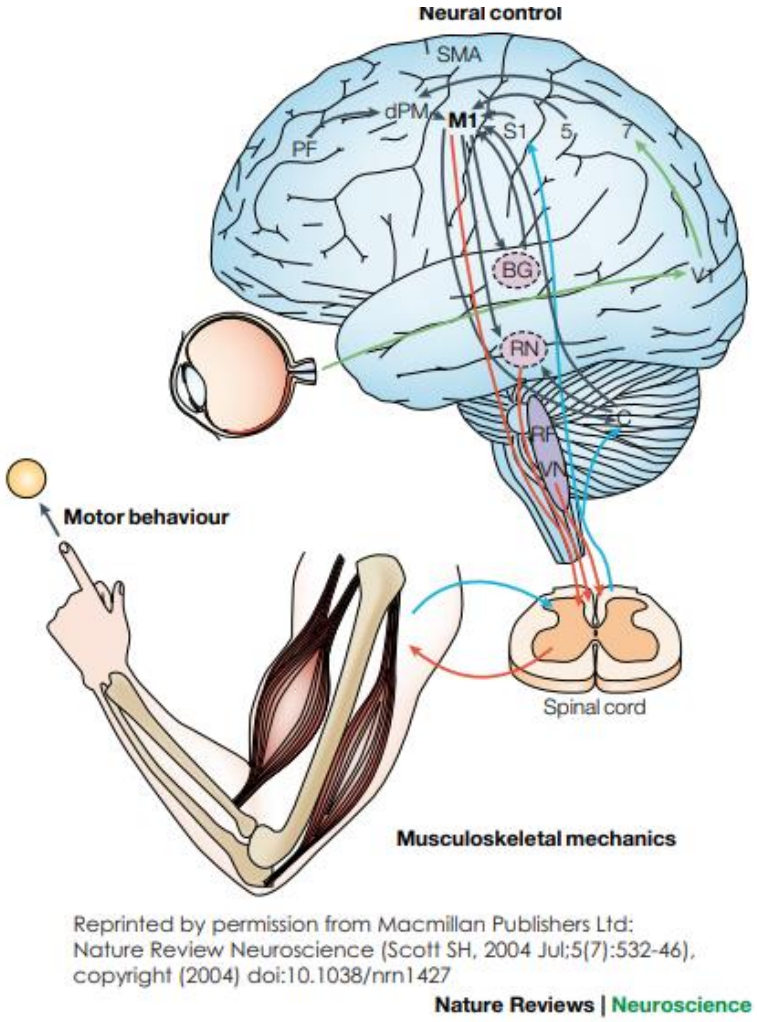
1. Eye fixation on the target
2. Saccadic eye movement to the target
3. Hand movement

→ **Vision precedes** hand movements

→ Vision is a **precursor of goal-directed actions**. → "**forward planning**"

→ **movement errors** occur when visual **feedback** is distorted

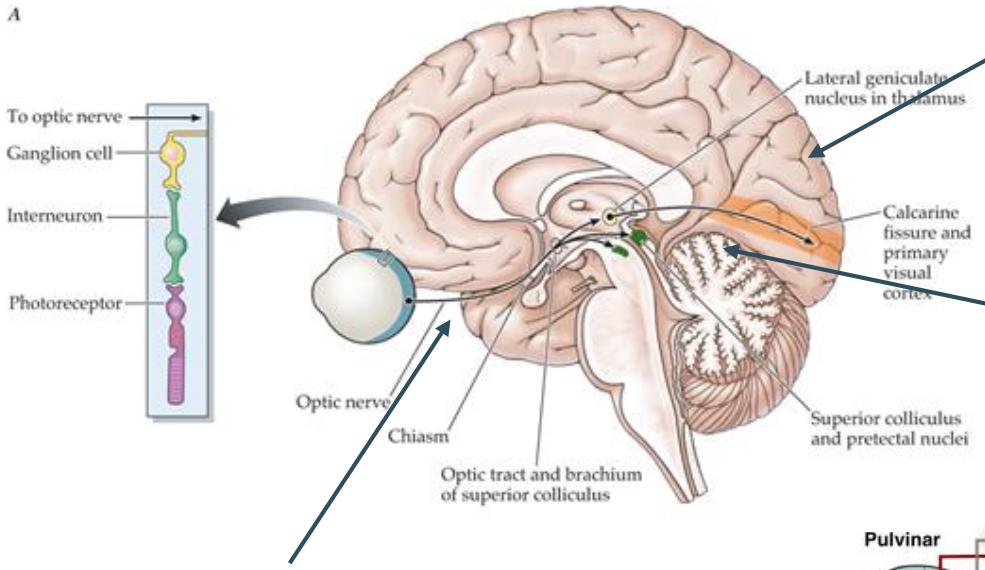
Vision is crucial in planning and performing movements



Nature Reviews | Neuroscience

Bekkering et al. (1995),Bagesteiro et al (2006)

Visual deficit in CP



Visual associative areas

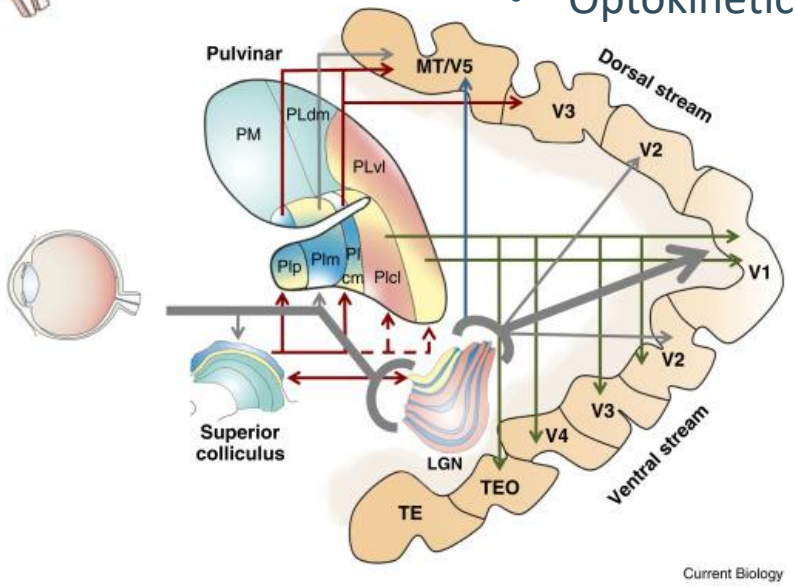
- Visual perception
- Visual-motor integration

Geniculostriate pathway

- Visual acuity
- Contrast sensitivity
- Stereopsis
- Visual field reduction
- Optokinetic nystagmus

Oculomotor dysfunction

- Fixation
- Saccades
- Pursuit
- Strabismus
- Nystagmus



Fazzi et al. (2012)

Vision and motor control in CP

- **Prolonged anticipatory gaze timing**
- **Prolonged MOA**

→ *impaired temporal coupling between eye and hand*

- **Increased frequency of gaze shift**

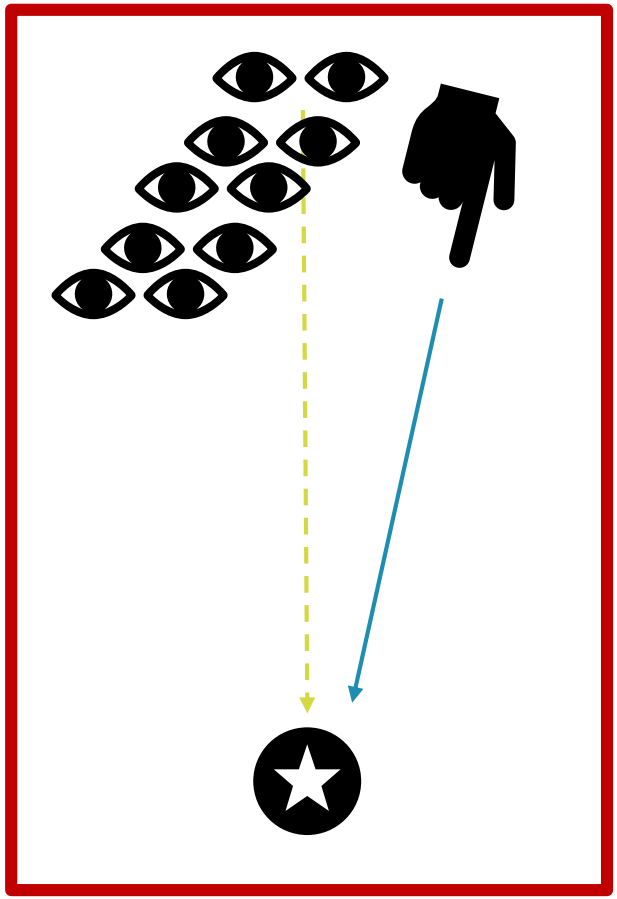
→ *lack of smooth pursuit* movements

→ *indicator of planning deficits*

- **Increased MT**

→ *deficits in the anticipatory vision*

→ *impaired visuomotor coordination*



Saavedra et al. (2009), Surkar et al (2018)

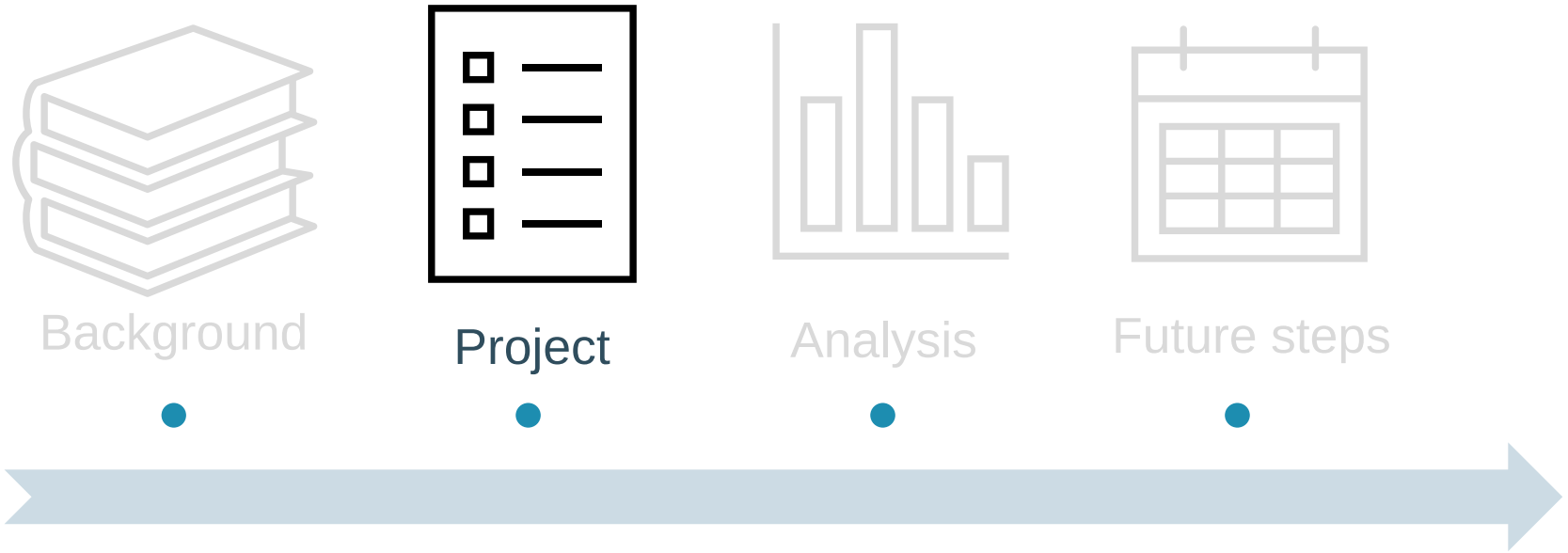
What is missing?

- Eye-hand coordination is crucial for ***forward planning***
- Studies on the role of vision on BMC deficits in children with uCP are
  - Limited to object grasp/manipulation
  - Mainly on unimanual functions
  - Mainly in an experimental setting

Swati et al. (2018); Saavedra et al. (2009), Surkar et al (2018)

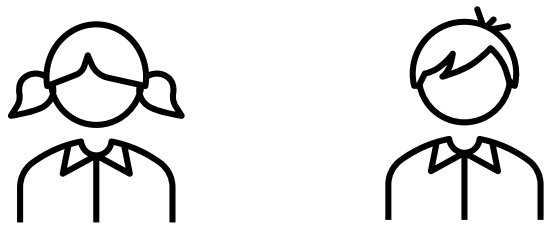
? Which is the impact of visual and oculomotor impairments on BMC in uCP

→ *Importance for therapeutic interventions on improving visuomotor coordination*


Background
Project
Analysis
Future steps

Sample

50 unilateral Cerabral Palsy (uCP)



50 matched typically developing children (TDC)

Age between 7 and 15

Individual matching based on

- **Age** (± 6M difference with CP child)
- **Sex**

Objectives

PART 1: Comprehensive assessment of behavioural visual function

A. In-depth investigation of visual functions in both uCP and TDC
B. Relations between clinical visual assessments and neuroimaging parameters (Systematic Review)

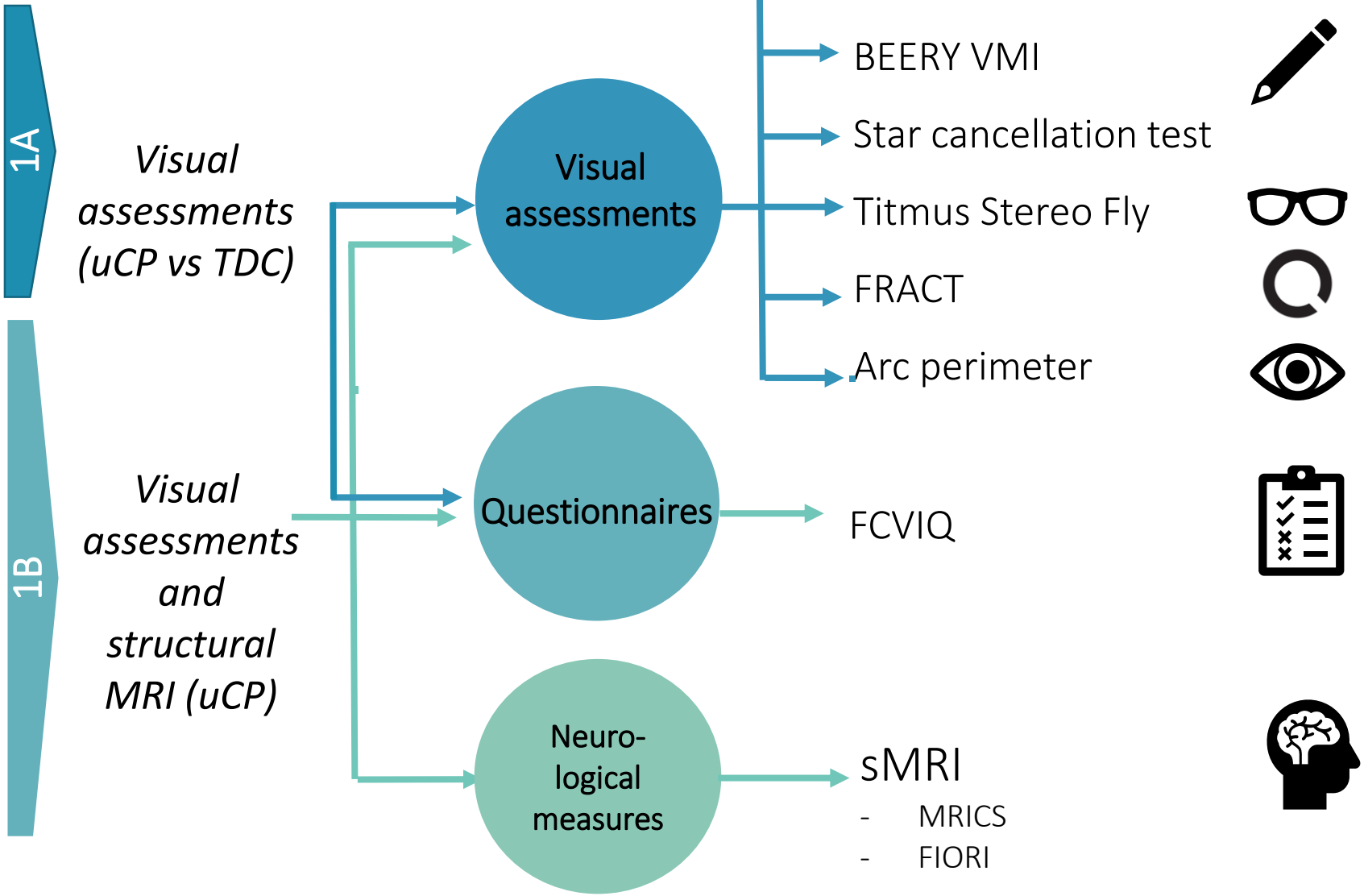
PART 2: Influence of visual function on bimanual measures

A. In-depth investigation of gaze using gaze-tracking system and KINARM Exoskeleton for bimanual motor control (BMC) in uCP and TDC
B. Relation between visual measures, BMC and functional hand use (uCP)

PART 3: Influence of neurological factors on visual and visuomotor control deficits

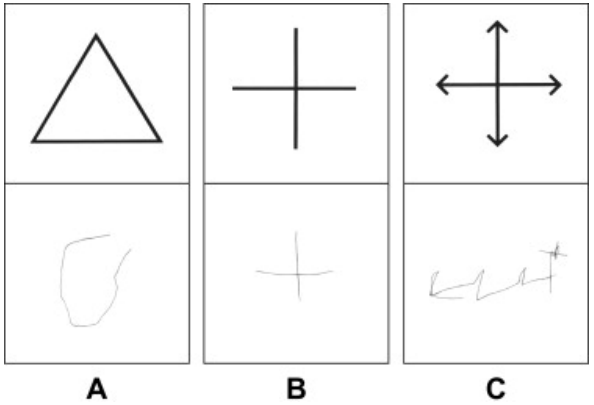
A. In-depth investigation of DWI data of the visual tracts in uCP
B. Relations between MRI data, clinical visual assessment and bimanual motor control tasks in uCP

Methods – PART 1

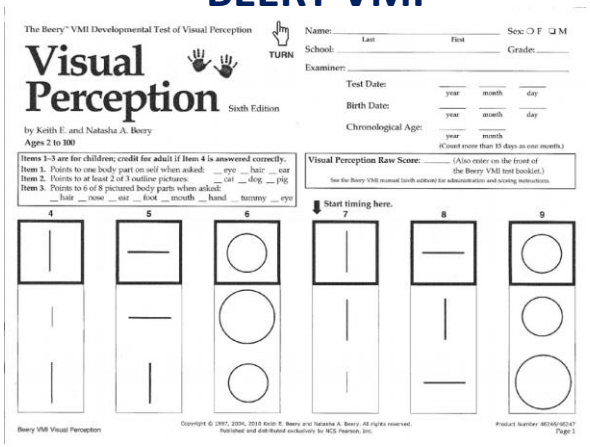


Methods – visual assessments

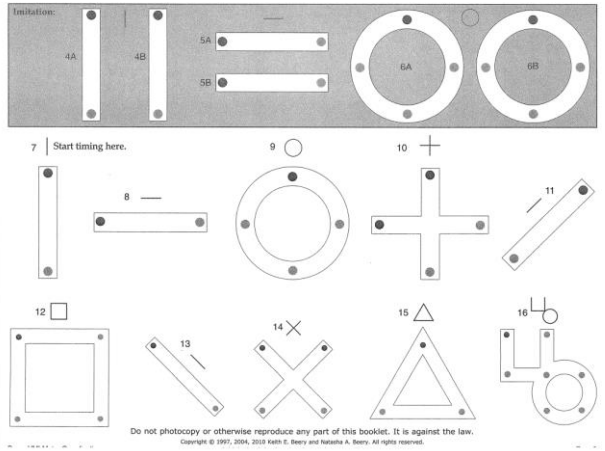
BEERY VMI



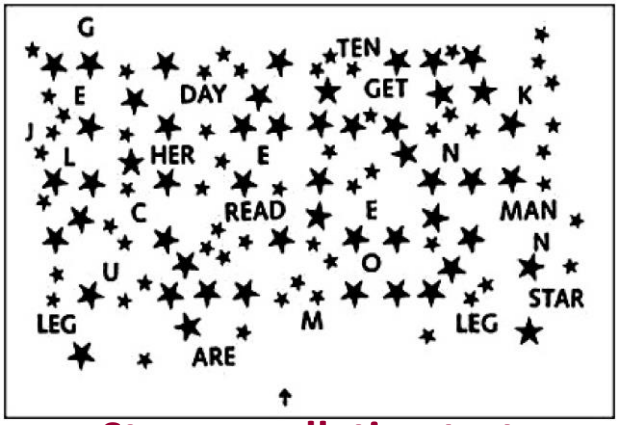
VMI



Visual Perception

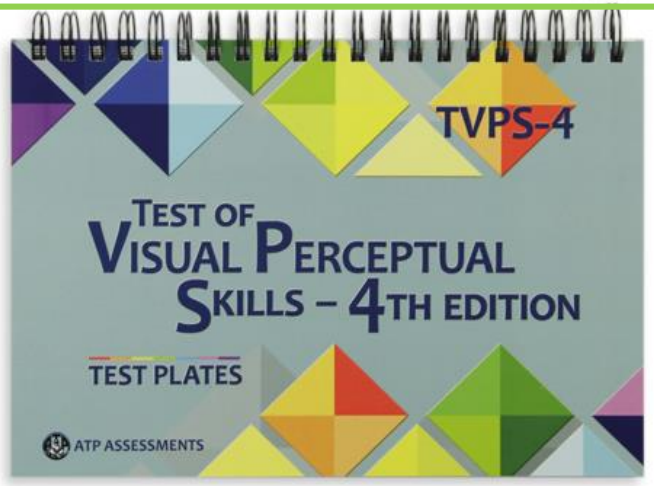


Motor coordination

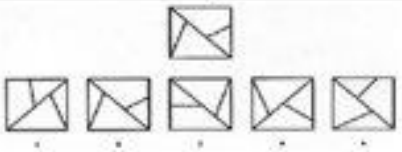
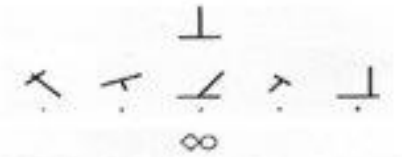
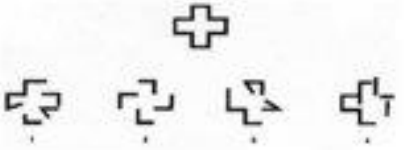


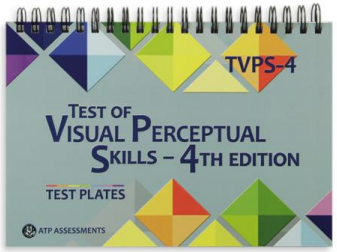
Star cancellation test

Neglect



TVPS

Visual skill	Example	Relavence
Visual Discrimination		– Ability to determine similarities between objects – needed for sorting objects eg Silverware, laundry
Visual Form Constancy		– recognize object despite change in size/ location
Visual Figure Ground		– find object of interest from background – finding milk in the fridge
Visual Closure		– fill in information to complete visual image – Finding objects in busy environment e.g. messy room
Visual Spatial Relations		– tell how objects relate to each other – Telling time on a clock
Visual Memory		– recall a visu – recognizing left in a room
Visual Sequential Memory		– recall a visu – phone numbers/ spelling



- Time constraints
- Fatigue and tiredness

Martin, N. A. (2017)

Methods – visual assessments

TITMUS STEREO FLY

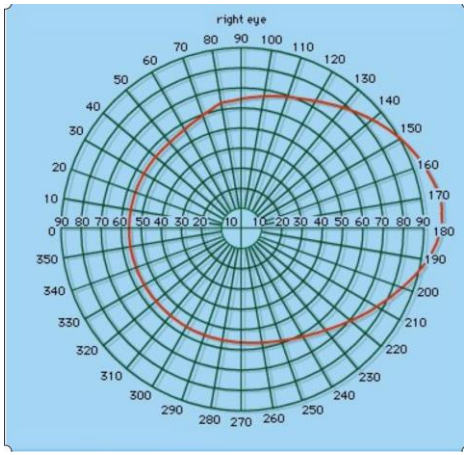
Stereopsis (3D)

FRACT

Visual acuity

Arc perimeter

Visual field

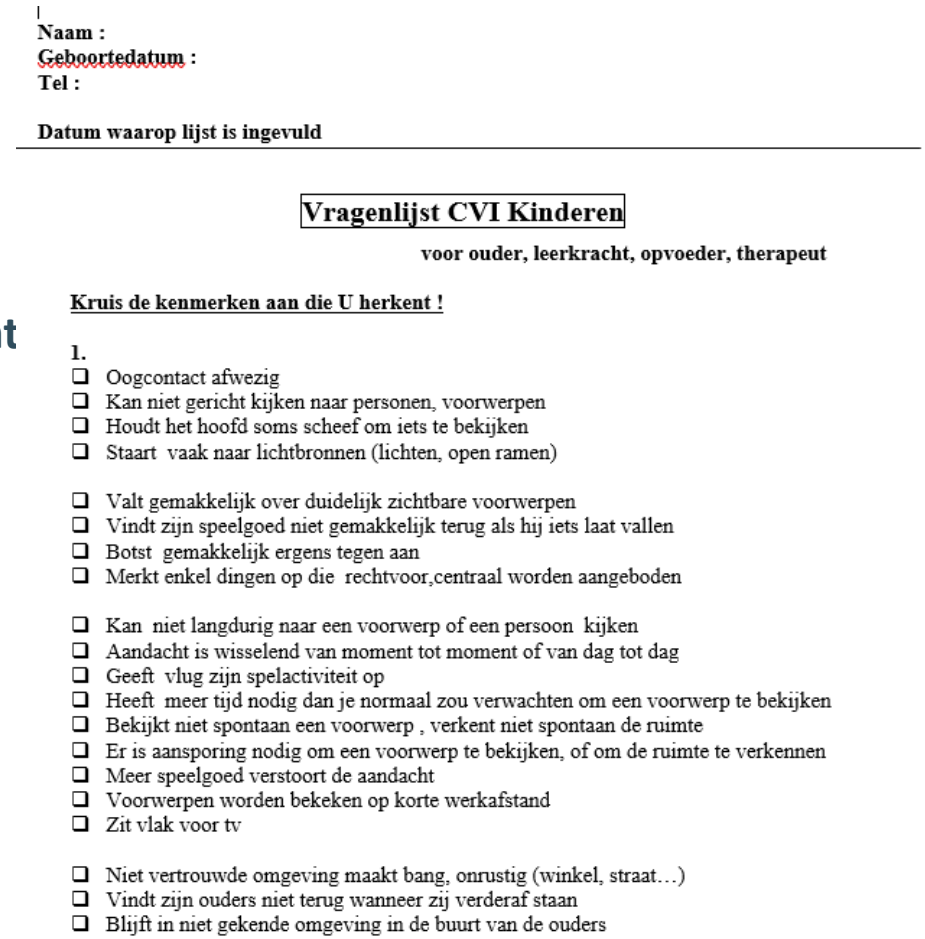


Methods – Flemish Cerebral Visual Impairment Questionnaire

Daily life visual behaviour screening tool

- 46-item binary (yes-no)
- Filled by caregivers
- 5 factors

1. **Object and face processing impairment**
2. **Visual (dis)interest**
3. **Clutter and distance viewing impairments**
4. **Moving in space impairments**
5. **Anxiety-related behaviour**



Naam :
Geboortedatum :
Tel :

Datum waarop lijst is ingevuld

Vragenlijst CVI Kinderen

voor ouder, leerkracht, opvoeder, therapeut

Kruis de kenmerken aan die U herkent !

1.

- ❑ Oogcontact afwezig
- ❑ Kan niet gericht kijken naar personen, voorwerpen
- ❑ Houdt het hoofd soms scheef om iets te bekijken
- ❑ Staart vaak naar lichtbronnen (lichten, open ramen)

- ❑ Valt gemakkelijk over duidelijk zichtbare voorwerpen
- ❑ Vindt zijn speelgoed niet gemakkelijk terug als hij iets laat vallen
- ❑ Botst gemakkelijk ergens tegen aan
- ❑ Merkt enkel dingen op die rechtvoor,centraal worden aangeboden

- ❑ Kan niet langdurig naar een voorwerp of een persoon kijken
- ❑ Aandacht is wisselend van moment tot moment of van dag tot dag
- ❑ Geeft vlug zijn spelactiviteit op
- ❑ Heeft meer tijd nodig dan je normaal zou verwachten om een voorwerp te bekijken
- ❑ Bekijkt niet spontaan een voorwerp , verkent niet spontaan de ruimte
- ❑ Er is aansporing nodig om een voorwerp te bekijken, of om de ruimte te verkennen
- ❑ Meer speelgoed verstoort de aandacht
- ❑ Voorwerpen worden bekeken op korte werkafstand
- ❑ Zit vlak voor tv

- ❑ Niet vertrouwde omgeving maakt bang, onrustig (winkel, straat…)
- ❑ Vindt zijn ouders niet terug wanneer zij verderaf staan
- ❑ Blijft in niet gekende omgeving in de buurt van de ouders

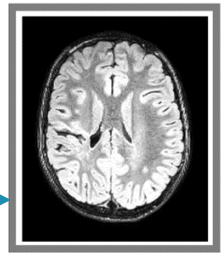
Ben Itzhak et al. (2020)

Methods – MRI Classification System

From Surveillance of Cerebral Palsy in Europe (SCPE)

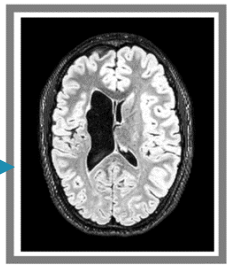
A	**Maldevelopments**	
	A1	Disorders of cortical formation (proliferation and/or migration and/or organization)
	A2	Other maldevelopments (among others: holoprosencephaly. Dandy-Walker malformation, corpus callosum agenesis, cerebellar hypoplasia…)
B	**Predominant white matter injury**	
	B1	Periventricular leucomalacia (PVL) (mild / severe)
	B2	Sequelae of intraventricular hemorrhage (IVH) or periventricular haemorrhagic infarction (PVHI)
	B3	Combination of PVL and IVH sequelae
C	**Predominant grey matter injury**	
	C1	Basal ganglia/thalamus (mild/moderate/severe)
	C2	Cortico-subcortical lesions only (watershed lesions in parasagittal distribution/multicystic encephalomalacia) not covered under C3
	C3	Arterial infarctions (middle cerebral artery/other)
D	**Miscellaneous** (examples: cerebellar atrophy, cerebral atrophy, delayed myelination, ventriculomegaly not covered under B, haemorrhage not covered under B, brainstem lesions, calcifications)	

A



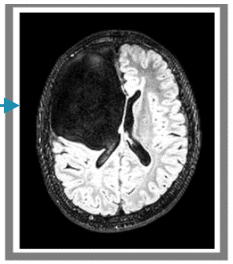
Maldevelopments

B



Periventricular white matter lesions

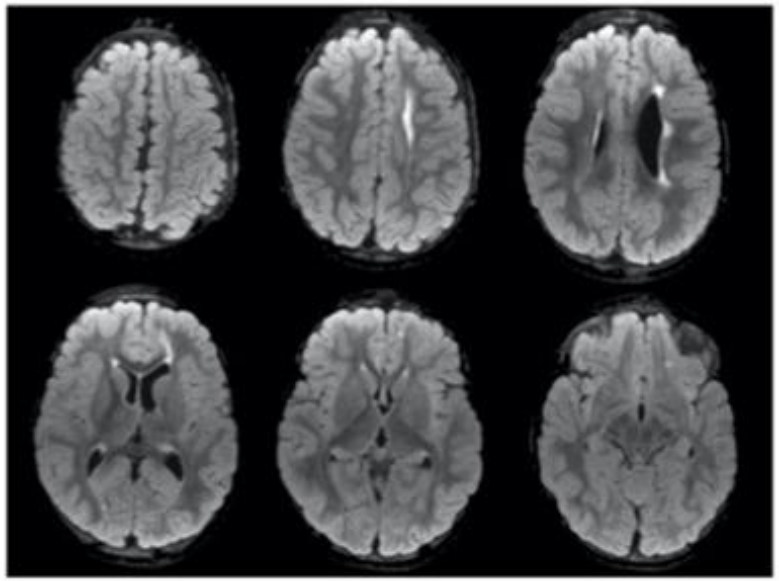
C

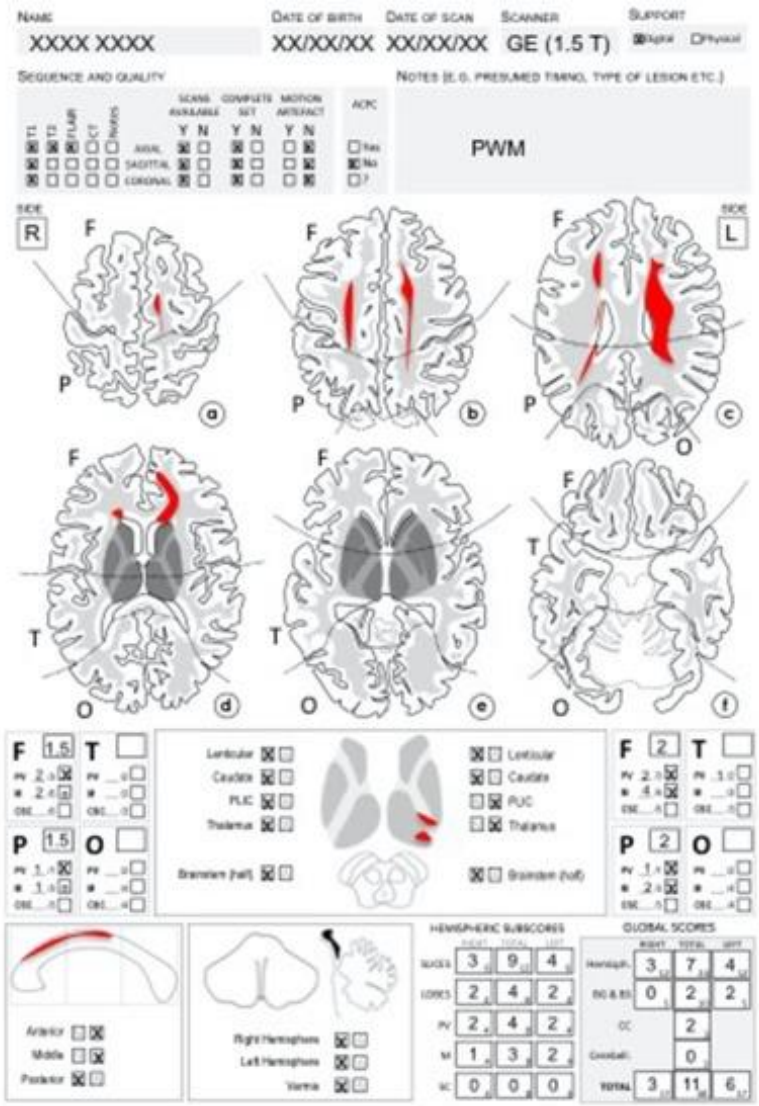


Cortical and deep grey matter lesions

Himmelmann et al. (2017)

Methods – Fiori scale





Fiori et al. (2014), Tinelli et al.(2020)

Methods – PART 2

2A

Eye movements and bimanual motor control (uCP vs TDC)

2B

Visual assessments and functional hand use (uCP)

BMC

- Kinarm Endpoint robot
- Box opening task

Eye movements

- Kinarm Gaze-tracker

Functional hand use

- Tyneside Pegboard Test (TPT)
- Assisting Hand Assessment (AHA)

Visual assessments

- TVPS
- BEERY VMI
- Star cancellation test
- Titmus Stereo Fly
- FRACT
- Arc perimeter

BMC = Bimanul Motor Control

Methods – Bimanual motor control

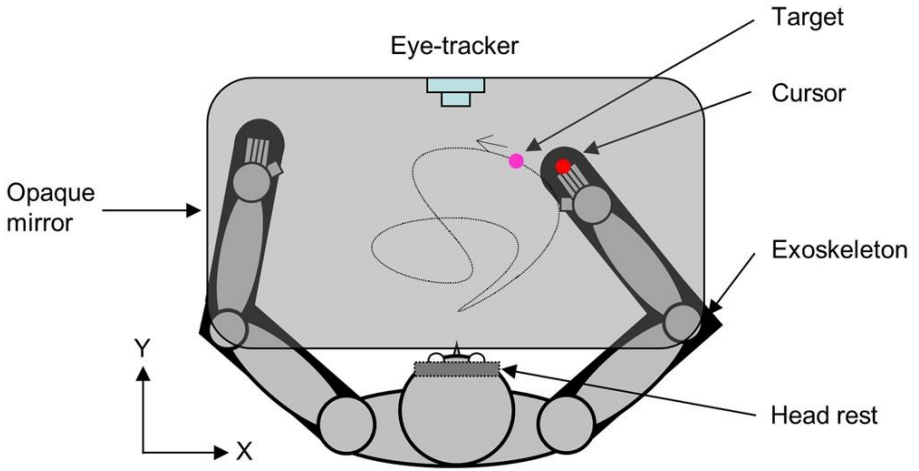
Kinarm Exoskeleton + gaze-tracker

Visuomotor

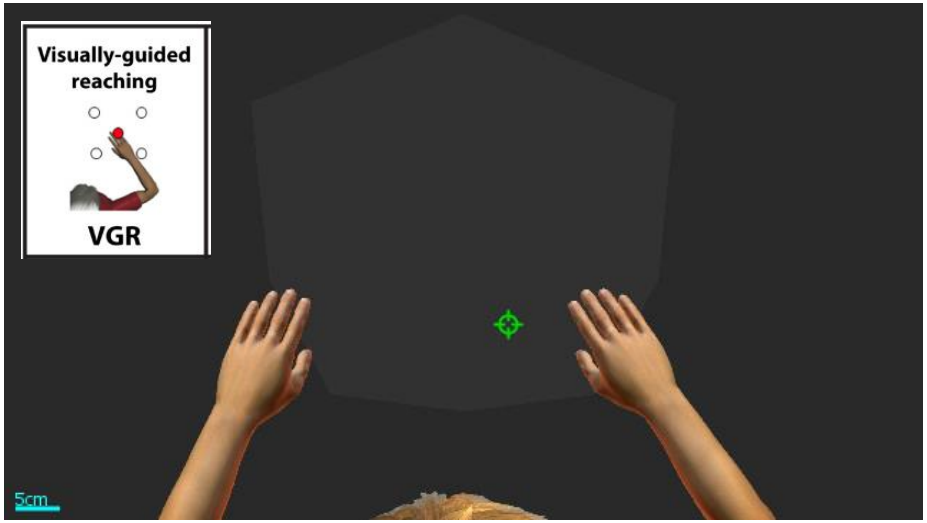
Visually-guided reaching	Ball-on-bar	Object hit
VGR	BOB	OH

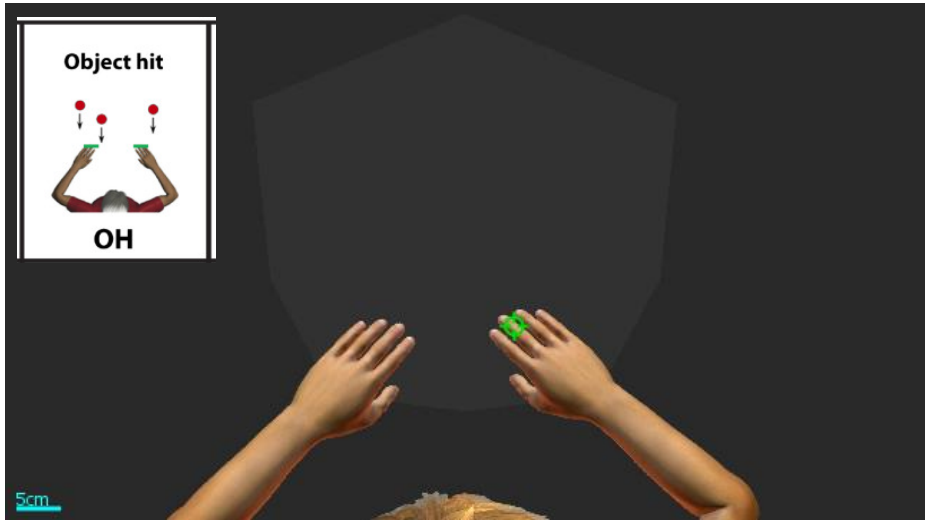
Bimanual coordination

Circuit task



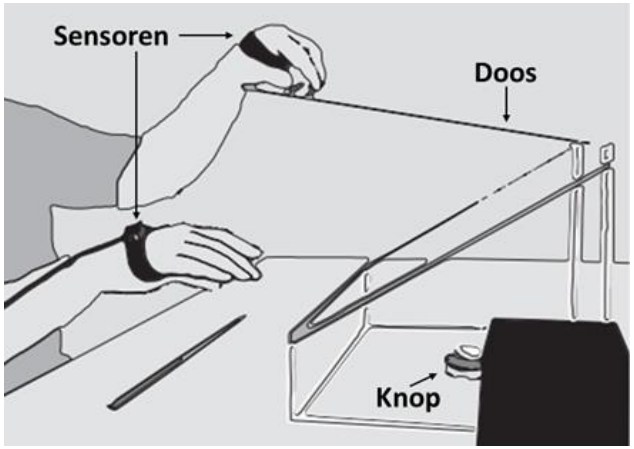
Kinarm Exoskeleton TASKS





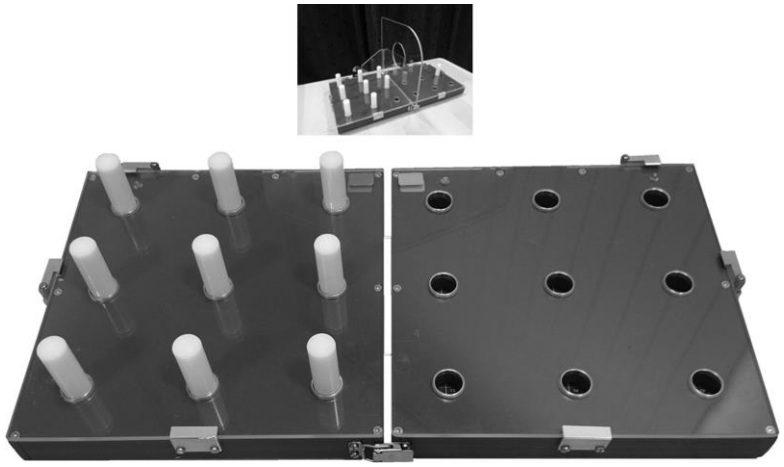
Methods – Bimanual measures

Bimanual motor control



Box opening task

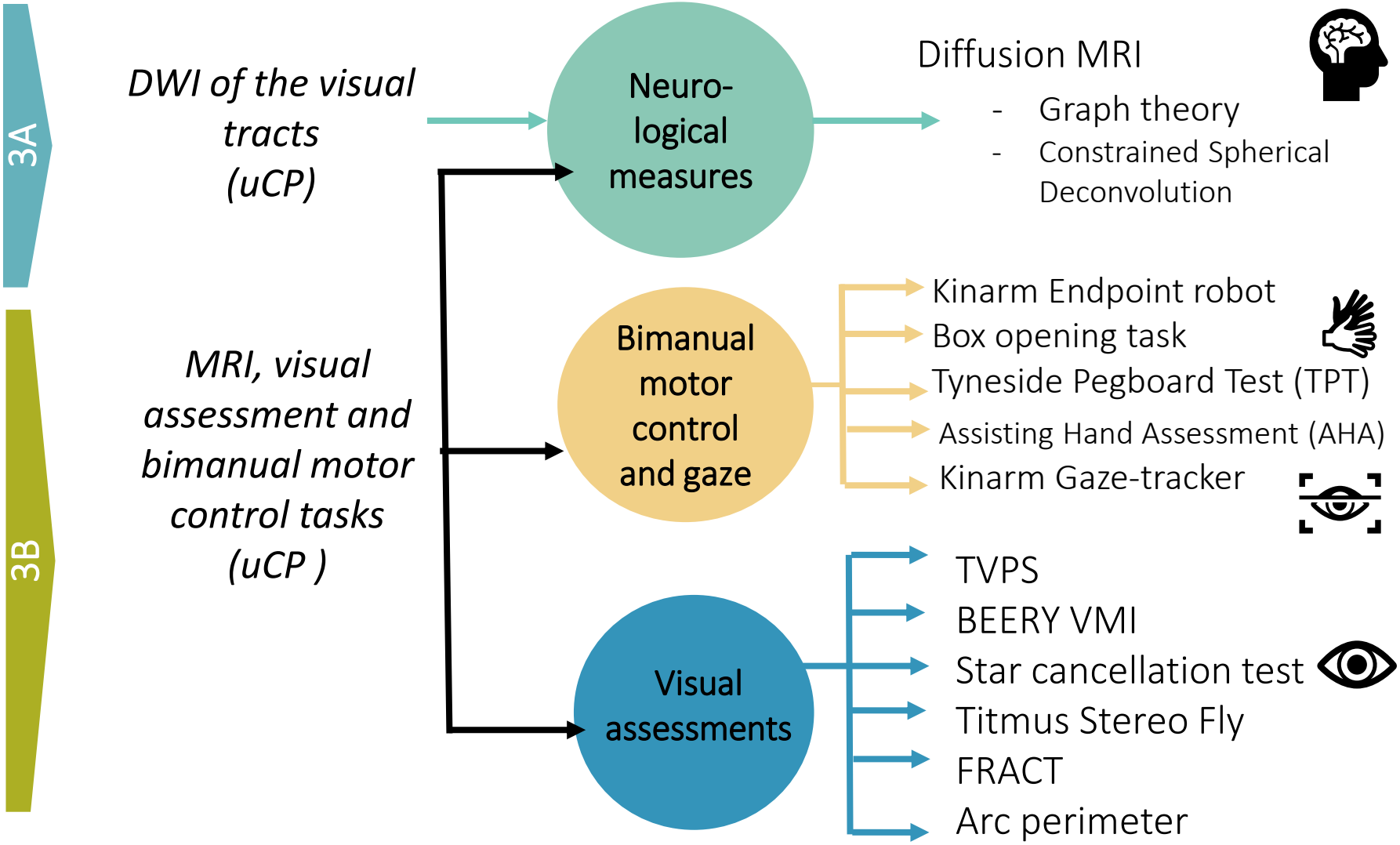
Functional hand use



Tyneside Pegboard Test (TPT)

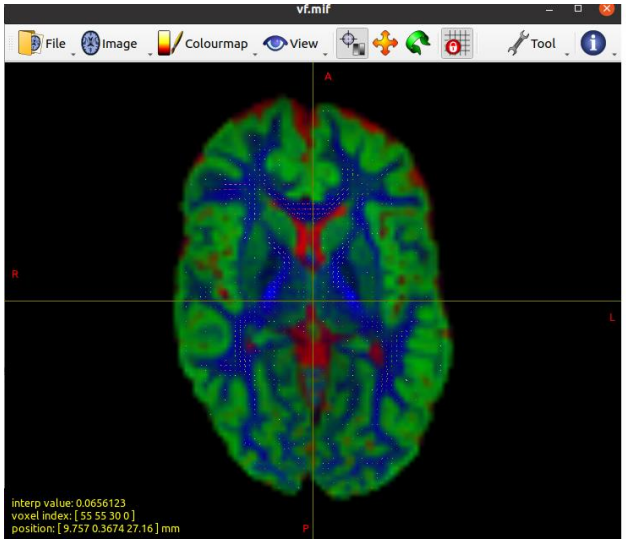
Assisting Hand Assessment (AHA)

Methods – PART 3

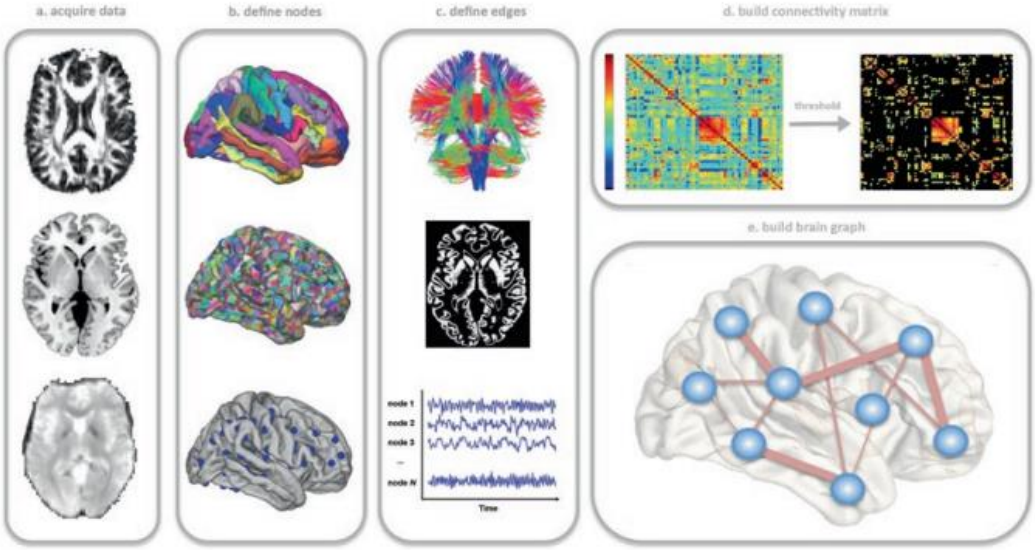


Methods – Diffusion MRI

Constrained Spherical Deconvolution



Graph Theory

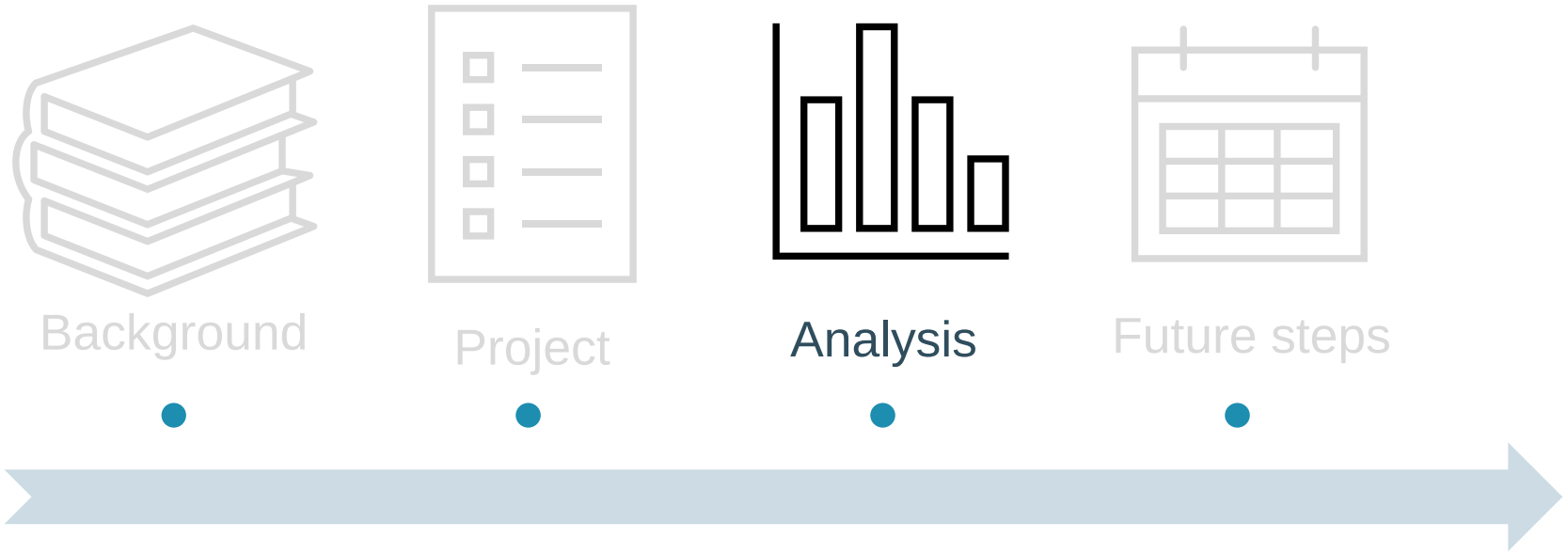


Fornito et al. (2016)

Methods – MRI lesion segmentation

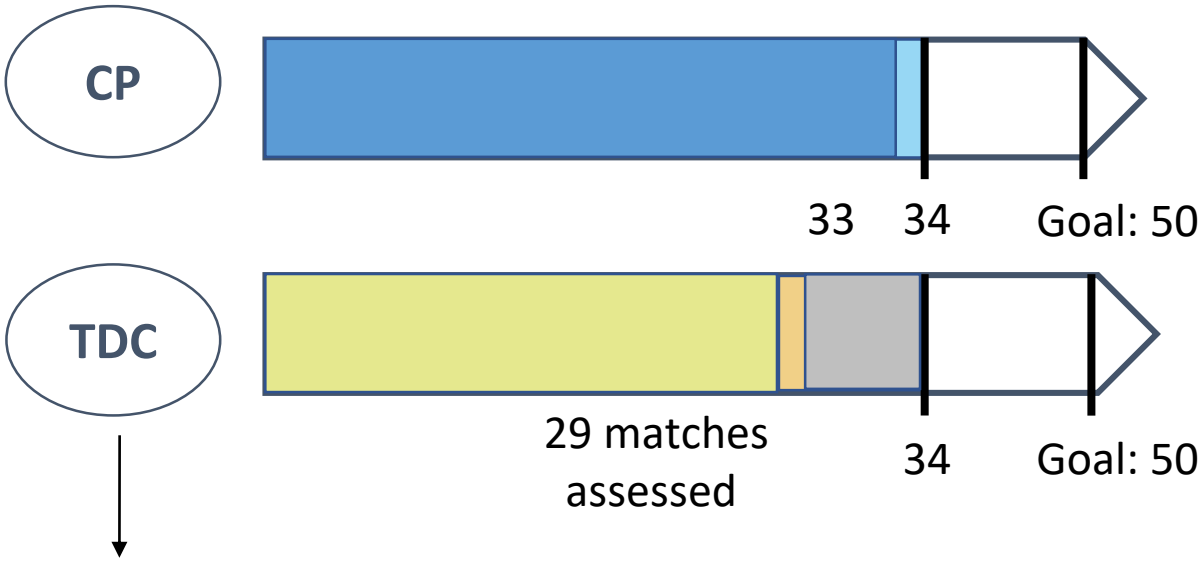
- Lesion segmentation to develop automatic classification

icometrix


Background
Project
Analysis
Future steps

Assessments – March 2022

SAMPLE: uCP and TDC – 7/15 y.o.



Individual matching based on

- Age (± 6M difference with CP child)
- Sex

CPB	TDC matched
CPB_01	TDC_01
CPB_02	TDC_08
CPB_03	TDC_23
CPB_04	TDC_42
CPB_05	TDC_12
CPB_06	TDC_27
CPB_07	
CPB_08	
CPB_09	TDC_30
CPB_10	TDC_04
CPB_11	TDC_05
CPB_12	TDC_19
CPB_13	TDC_32
CPB_14	TDC_34
CPB_15	TDC_25
CPB_16	TDC_03
CPB_17	TDC_36
CPB_18	TDC_28
CPB_19	TDC_17
CPB_20	TDC_38
CPB_21	TDC_09
CPB_22	TDC_31
CPB_23	TDC_40
CPB_24	TDC_37
CPB_25	TDC_33
CPB_26	TDC_07
CPB_27	TDC_29
CPB_28	TDC_39
CPB_29	TDC_02
CPB_30	TDC_41
CPB_31	TDC_21
CPB_32	TDC_13
CPB_33	
CPB_34	

Missing data

Data type	Assessment	#
Bimanual motor control	*KINARM*	1
	Box opening task	7
Neurological	*MRI*	8
Visual	*TVPS*	2

Home administration of **9/11 TVPS** (August 2021)

Preliminary analysis – clinical measures uCP

Data	Cut-off	Total data	# <cut-off	% impaired uCP
TVPS_DIS	*<9 perc*	29	9	**31**
TVPS_SPA	*<9 perc*	29	7	**24**
TVPS_CON	*<9 perc*	29	6	**21**
TVPS_FGR	*<9 perc*	29	8	**28**
TVPS_CLO	*<9 perc*	29	9	**31**
Beery_VMI	*<9 perc*	29	11	**38**
Beery_VP	*<9 perc*	30	9	**30**
Beery_MC	*<9 perc*	30	19	**63**
FRACT_both	*< 0.4 VA*	25	1	**4**
FRACT_Right	*< 0.4 VA*	25	1	**4**
FRACT_Left	*< 0.4 VA*	25	2	**8**
Arc_R.nas	*< 60*	30	24	**80**
Arc_R.lat	*< 90*	30	25	**83**
Arc_R.up	*< 60*	30	28	**93**
Arc_R.down	*< 70*	30	26	**87**
Arc_L.nas	*< 60*	30	24	**80**
Arc_L.lat	*< 90*	30	25	**83**
Arc_L.up	*< 60*	30	29	**97**
Arc_L.down	*< 70*	30	27	**90**

TVPS
- Scored 29/33

BEERY
- Scored 30/33

FRACT
- Scored 25/33

ARC PERIMETER
- Scored 26/33

Menken et al. (1987); Tsai et al. (2009); Jongmans et al. (1996); Kozeis et al. (2007)

Preliminary analysis

PART 1: Visual functions

A. Clinical visual assessments in uCP

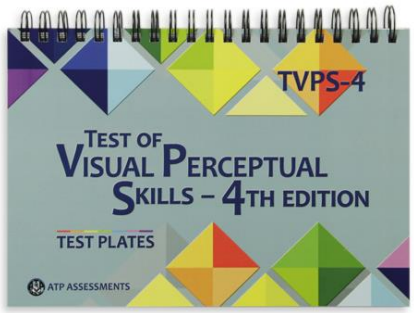
Relation between TVPS and FCVIQ ?

→ *SPSS and R analysis*

a. Normality of data (SPSS)

b. Non-parametric Spearman correlation (SPSS)

c. Scatterplot results in R



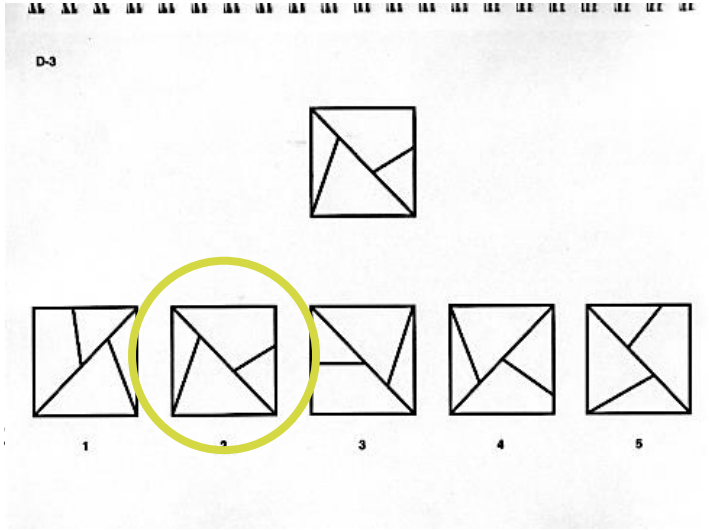
TVPS subtest

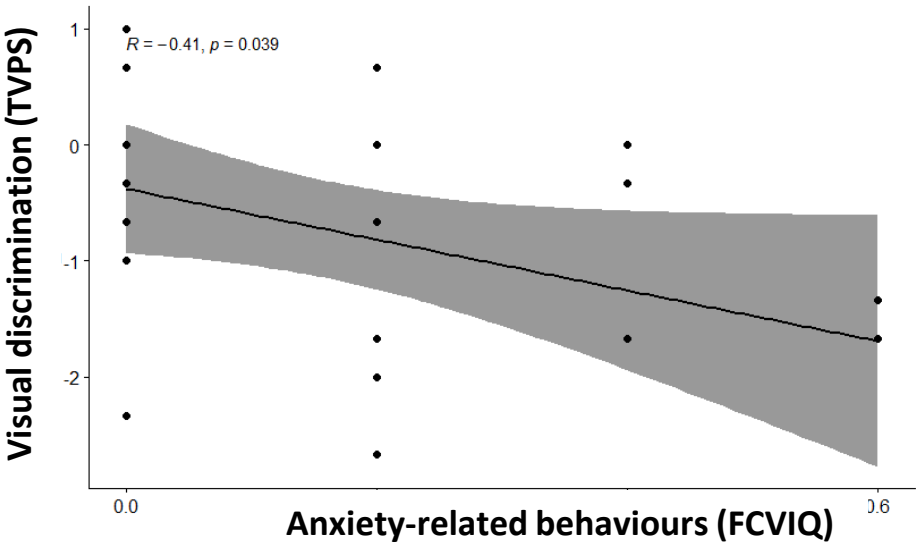
1. *Visual discrimination*
2. *Visual spatial relations*
3. *Visual form constancy*
4. *Visual figure-ground*
5. *Visual closure*

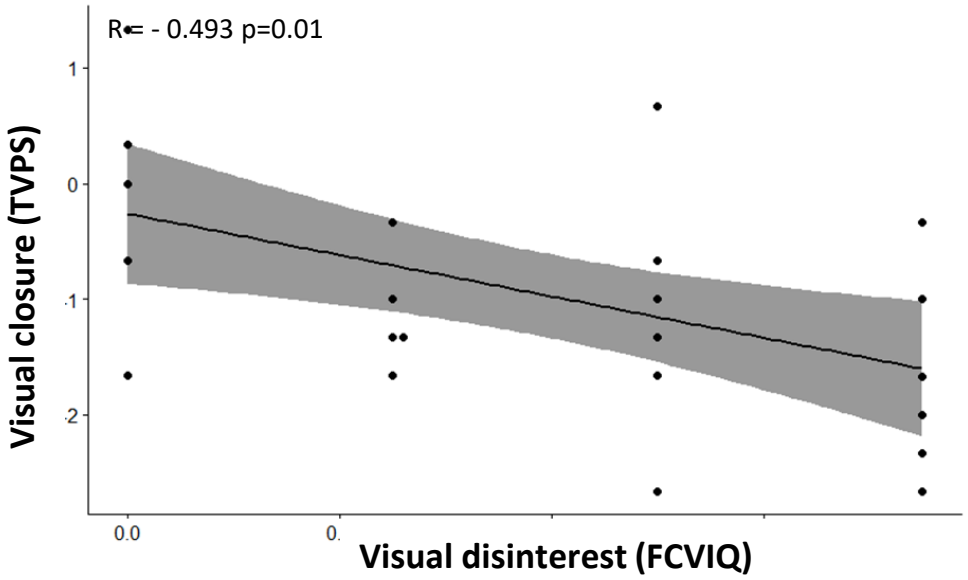
FCVIQ factors

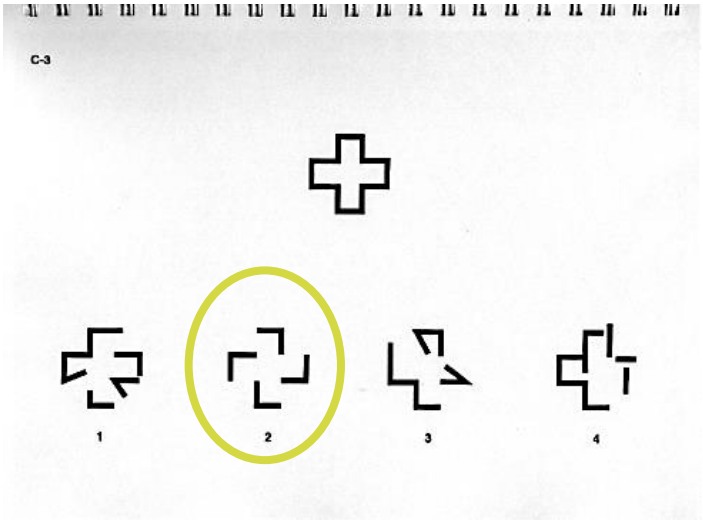
1. *Object and face processing impairments*
2. *Visual (dis)interest*
3. *Clutter and distance viewing impairments*
4. *Moving in space impairments*
5. *Anxiety-related behaviour*

Preliminary analysis – Correlation results



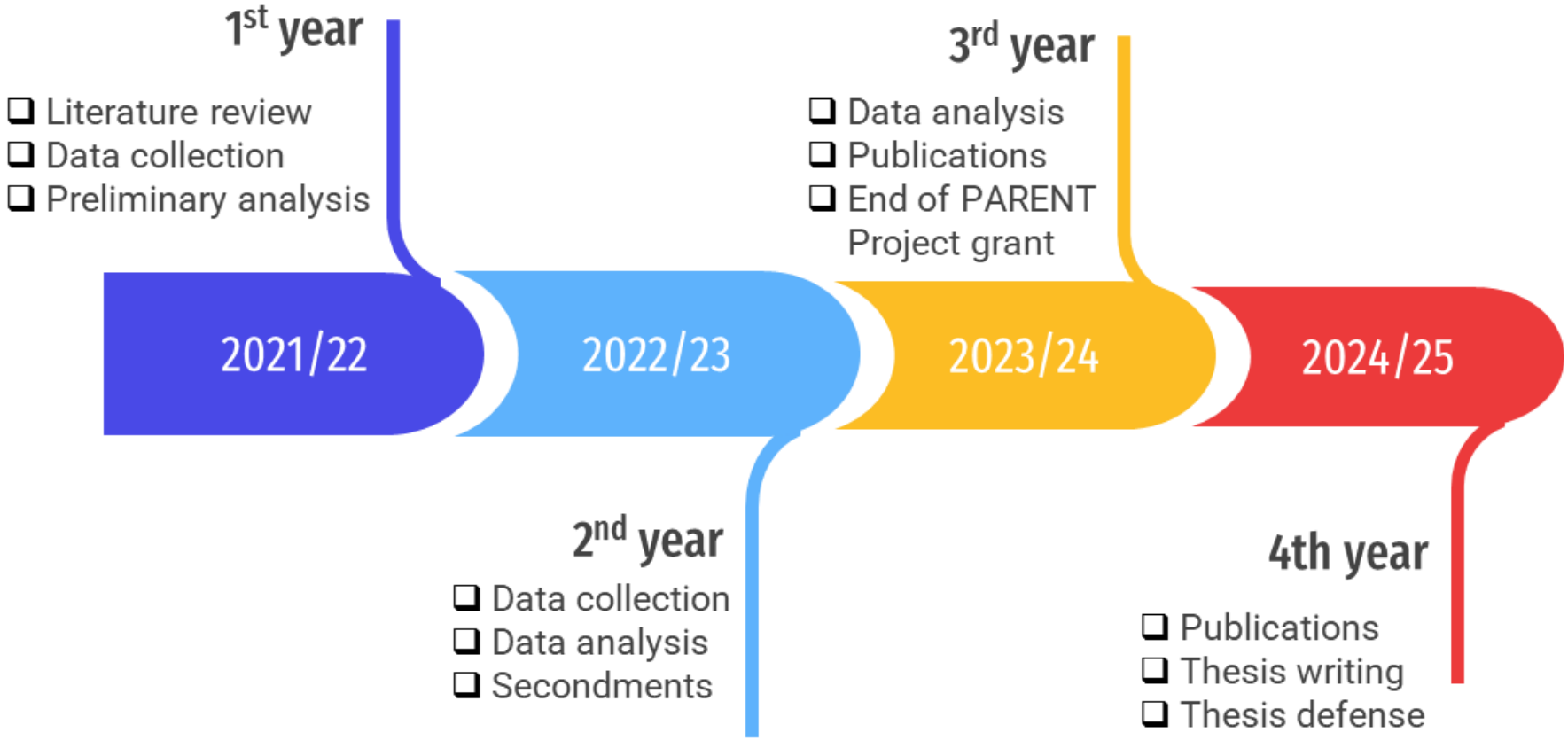







Background
Project
Analysis
Future steps

Project goals



Future research steps

Ongoing

- Assessments uCP/TDC
- Analysis of visual assessments (uCP/TDC) and sMRI scoring (uCP)
- Lesion segmentation (collab with Icometrix)
- Systematic Review (medicine master student)

From the summer

DWI analysis

- *Preprocessing with MRTRix*
- *Graph theory/CSD*

January 2023

Gaze-tracker

ITN Training schools

- *1st Training School – Cadiz, October 2021*
- *2nd Training School – Leuven, 31.03.2022/02.04.2022*
- *3rd Training School – Lubjana, September 2022*

ITN secondments

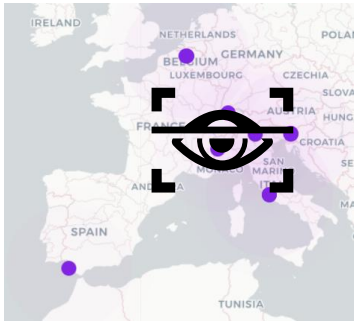
UCA

UNIVERSIDAD DE CADIZ
Spain
WEBSITE

1. UN
- **W**
- **Ob**

Neurological assessments and analysis – link with visual test

- ❑ Pediatrics MRI classification (manual and automatic)
- ❑ ROI analysis and TDST analysis of DTI
- ❑ Possibility to join clinical visits
- ❑ Integration of visual assessment/ questionnaires of our



Eye-tracker assessment and analysis

2. UN
- **W**
- **Objectives**
  - ❑ Eye-tracker technology in children
  - ❑ Eye-tracker analysis techniques

Univerza v Ljubljani

UNIVERZA V LJUBLJANI
Slovenia
WEBSITE

GPI

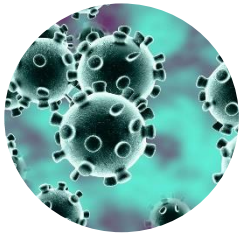
3. GPI –
- **Wh**
- **Obj**
  - ❑ Pattern recognition analysis implemented on clinical data

AI technology: integration of different assessments

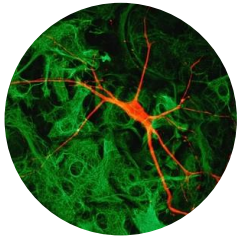
GPI SPA
Italy
WEBSITE

PhD requirements

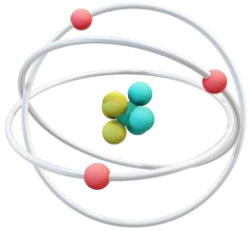
DOCTORAL TRAINING



TRUNCUS COMMUNIS



THEMATIC PROGRAM CMN



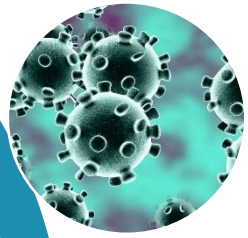
Transferable skills training

Career development

PhD requirements

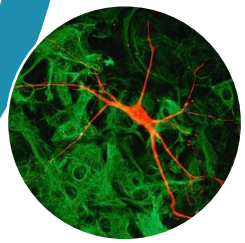
PARENT Training school (Cadiz, Oct 2021)

Doctoral training



TRUNCUS COMMUNIS

- ✓ International meeting (≥1)
- ✓ Research integrity I
- ❑ Attend seminars (≥15)
- ❑ Scientific article (≥1)
- ❑ Research seminar
- ❑ Research integrity II
- ❑ Progress reports in Toledo



THEMATIC PROGRAM CMN

- ❑ **10 neuroscience seminars per year**
- ❑ **8 Journal clubs per year**

PhD requirements

Transferable skills training

Communication	• Dutch as a foreign language (Intro) • CLT. A1
Scientific tools	• Matlab supercalculator • Introduction Fundamental statistical methods SPSS • Matlab supercalculator – Programming • Excel: tips and tricks

Career development

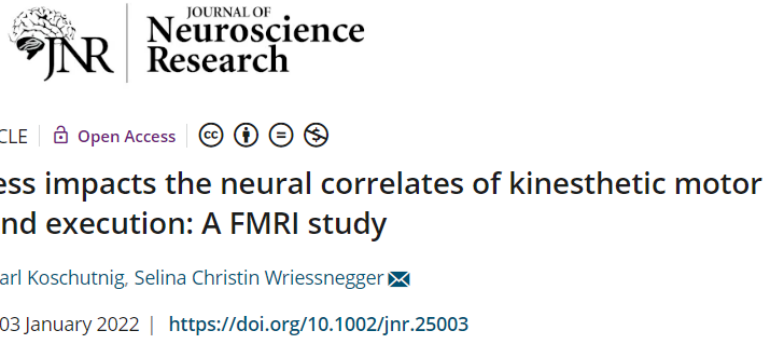
Career	• Brand your career profile
Didactic Training	• Supervising a Master's Thesis

- January 2022 – first master student
- Currently supervising 3 master students

Achievements

✓ **First author publication** – *January 2022*

Crotti, M., Koschutnig, K., & Wriessnegger, S. C. (2022).
Handedness impacts the neural correlates of kinesthetic motor imagery and execution: A FMRI study.
Journal of Neuroscience Research.

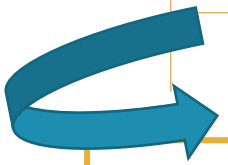


✓ **Poster presentation accepted** – *EACD 2022* (Barcelona, Spain)

The relation between visuoperceptual impairments and visual behaviour in daily life in children with unilateral cerebral palsy

PhD requirements – further courses/events

Month	Course	Date	Institution
Mar-22	Writing Skills for Biomedical Researchers course	15.03.22 22.03.22 29.03.22	*KU Leuven*
	23ThingsInternartional https://www.23thingsinternational.com/things	14.03.22	*Several partenrs*
	Creating effective poster presentation	21.03.22	*Dr Jean-luc Doumont*
ITN Training school Leuven	Poster presentation practice and feedback	31.02.22	*KU Leuven*
	Writing skills – feedback	02.04.22	*KU Leuven*
Apr-22	Deliver your presentation remotely	29.04.22	*Dr Jean-luc Doumont*
May-22	Systematic review	9-11.05.22	*KU Leuven*
Jun-22	Poster presentation course	03.06.22	*KU Leuven*



Thank you for your attention

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KU Leuven, Belgium

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Missing data

PART 2: Influence of visual function on BMC

A. Eye Gaze-tracking and Kinarm Exoskeleton in uCP and TDC

⇒ uCP: 29 children

⇒ TDC: 35 children

B. Relation between visual measures and bimanual motor control (both uCP and TDC)

⇒ uCP: 22 children

⇒ TDC: 35 children

Missing data

PART 3: Influence of neurological factors on visual and visuomotor control deficits

B. Relations between MRI data, clinical visual assessment and bimanual motor control tasks in uCP

⇒ Box opening : 23 uCP
⇒ Kinarm: 29 uCP
⇒ Visual functions : 29 u CP
⇒ MRI : 24 uCP
⇒ TMS (?)

---- complete dataset uCP