Duchenne & the brain

Sam Geuens, PhD
Neuropsycholoog
NMRC Pediatrie, UZ Leuven

Cognition and behaviour in DMD

- Duchenne De Boulogne (1861)
  "Boys with dull intellect and difficult speech"

- Intelligence
  - Average 1 SD below population mean
  - Discrepance between skills

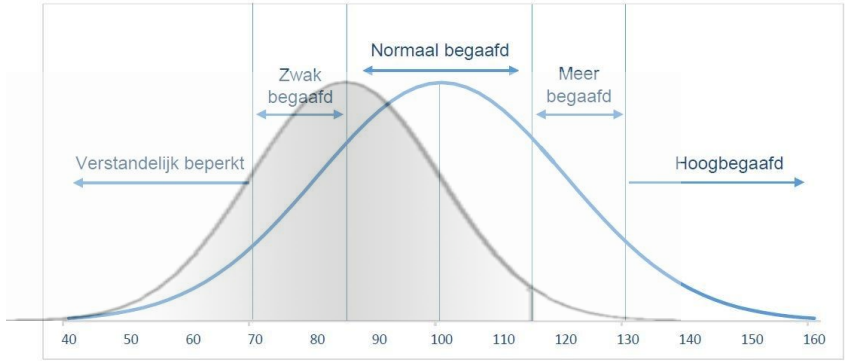
- Working memory
  - Verbal working memory

- Language

- Implicit/procedural learning

- Academic learning problems

- Behavioral and psychiatric difficulties



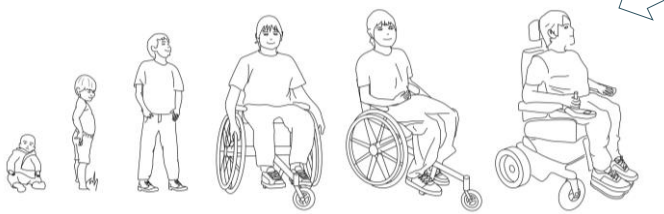
Duchenne muscular dystrophy

dystrophin gene

(X-chromosome)

Disrupted production of dystrophin protein

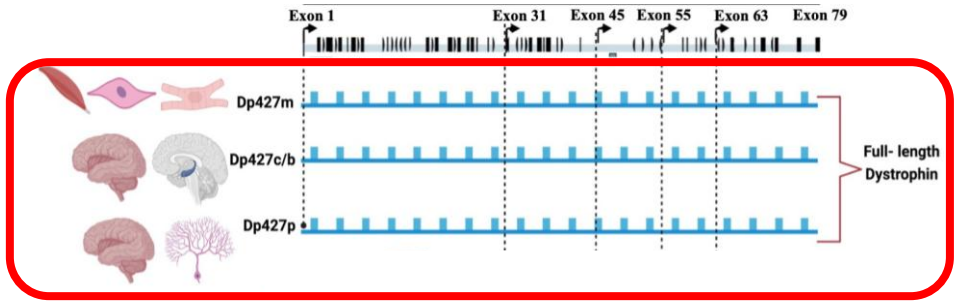
Muscles



Picture designed by Justus Kuijer

Dystrophin gene

1	2	3	4	5	6	7	8	9	10	11
12	13	14	15	16	17	18	19	20	21	22
23	24	25	26	27	28	29	30	31	32	33
34	35	36	37	38	39	40	41	42	43	44
45	46	47	48	49	50	51	52	53	54	55
56	57	58	59	60	61	62	63	64	65	
66	67	68	69	70	71	72	73	74	75	
76	77	78	79							



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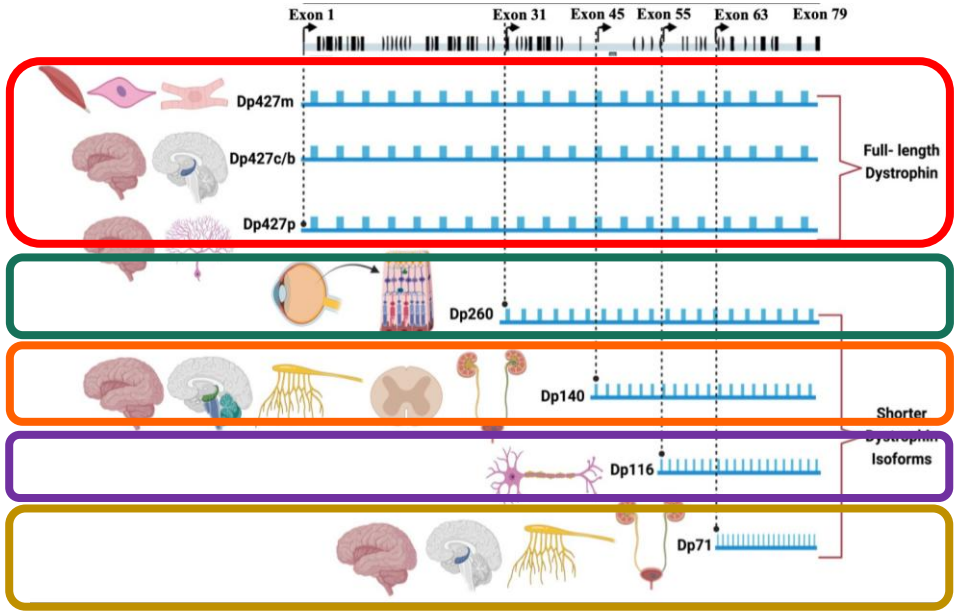
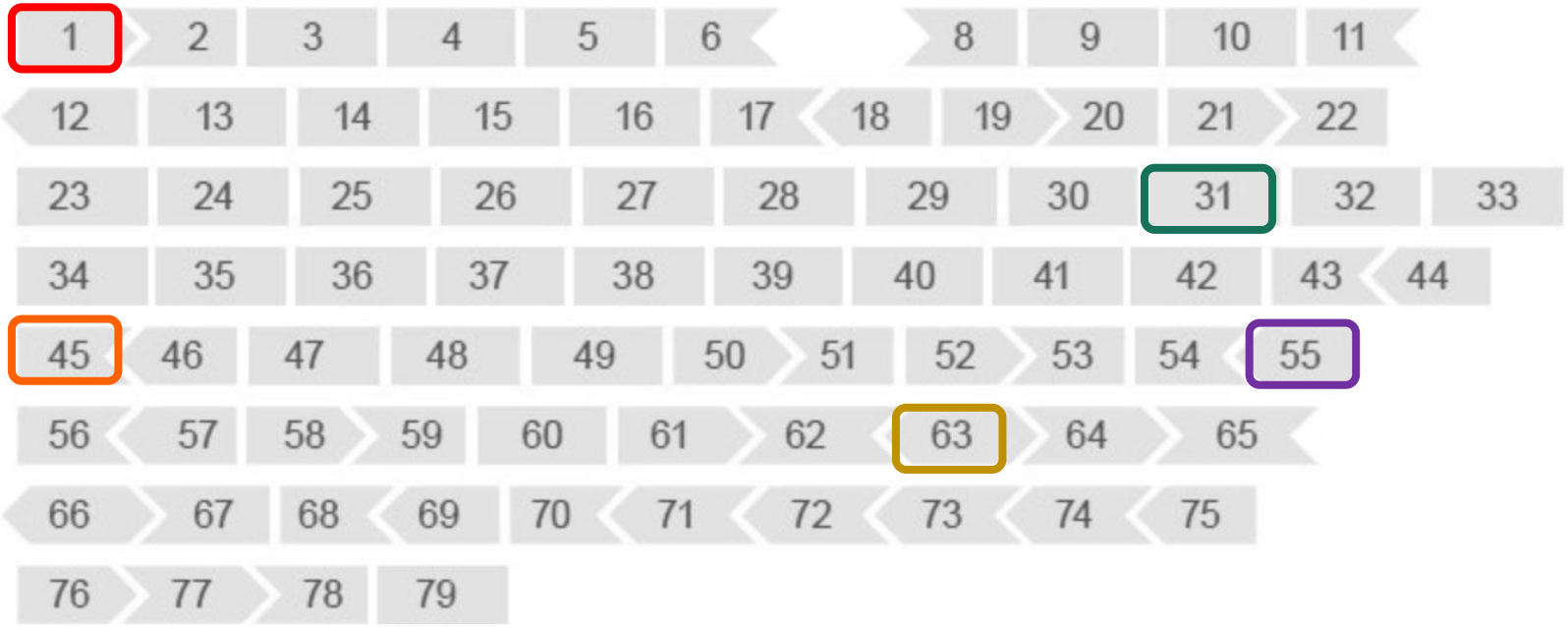
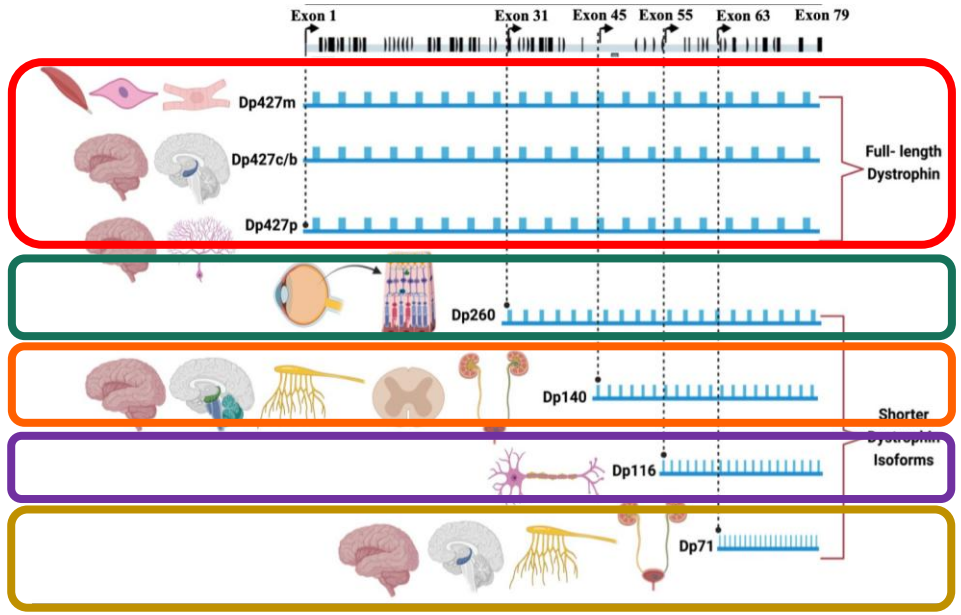
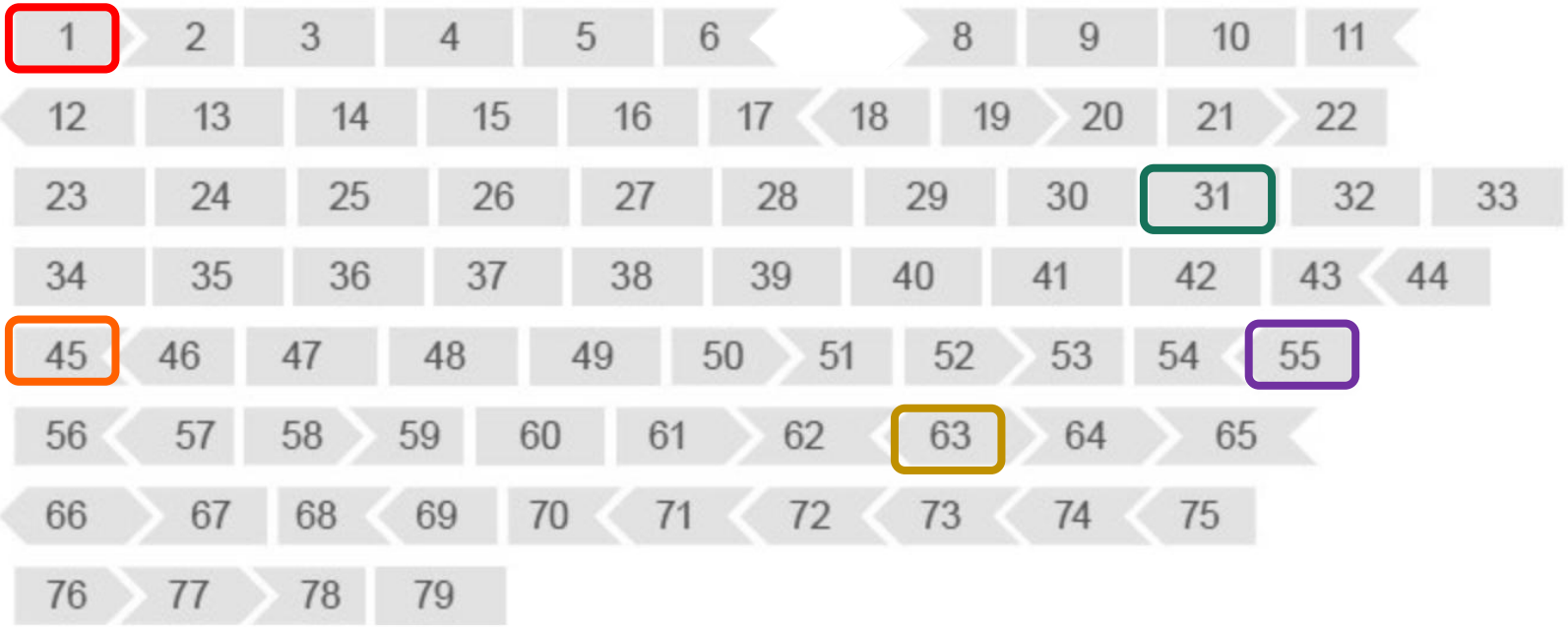


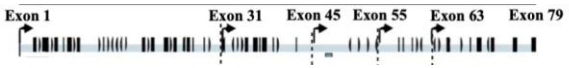
Dystrophin gene

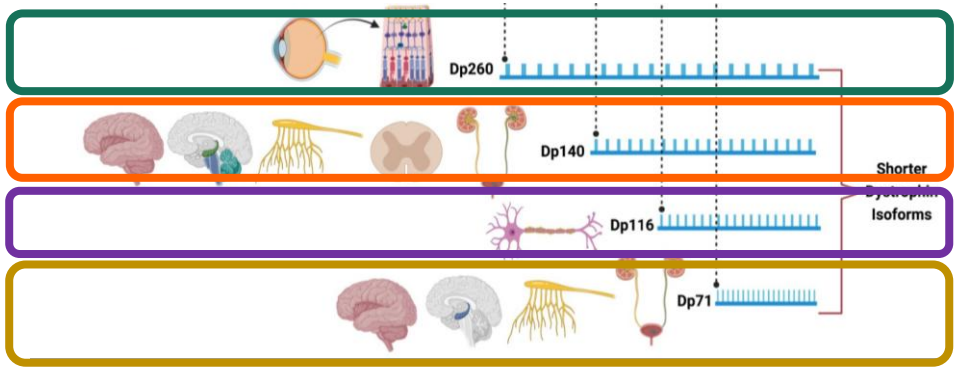




Dystrophin gene







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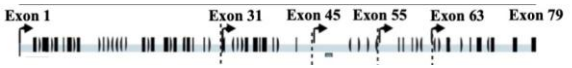

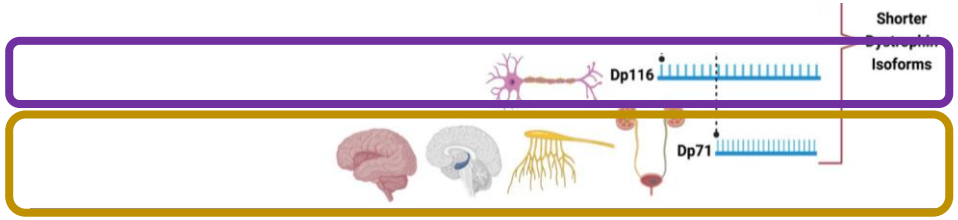

Dystrophin gene

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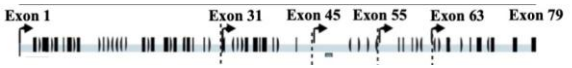
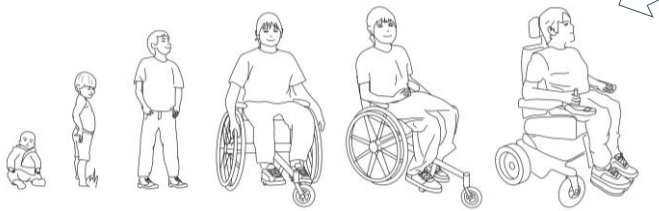


Duchenne muscular dystrophy

dystrophin gene
(X-chromosome)

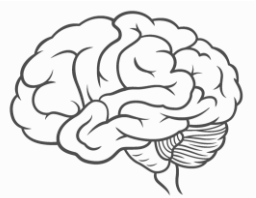
Disrupted production of dystrophin protein

Muscles



Picture designed by Justus Kuijer

Brain



Neurobehavioral difficulties:

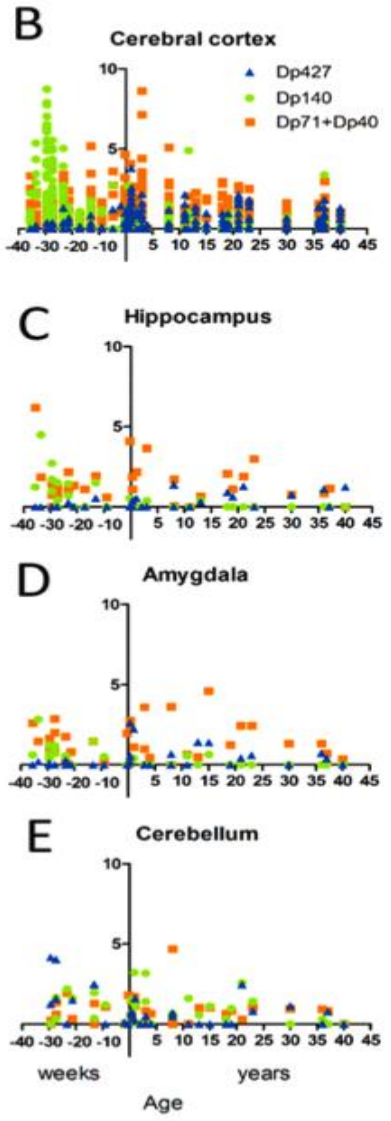
- Cognition[1]
- Working memory[1]
- Implicit learning[1]
- Academic learning[1]
- Behavior[1]
- …

[1]Darmahkasih (2020), Doorenweerd

Dystrophin isoforms

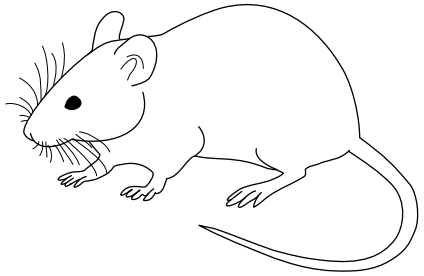
Different dystrophin isoforms are expressed in different brain regions during various periods of brain development:

- prenatal development
- neonatal development
- childhood
- adolescence
- adulthood



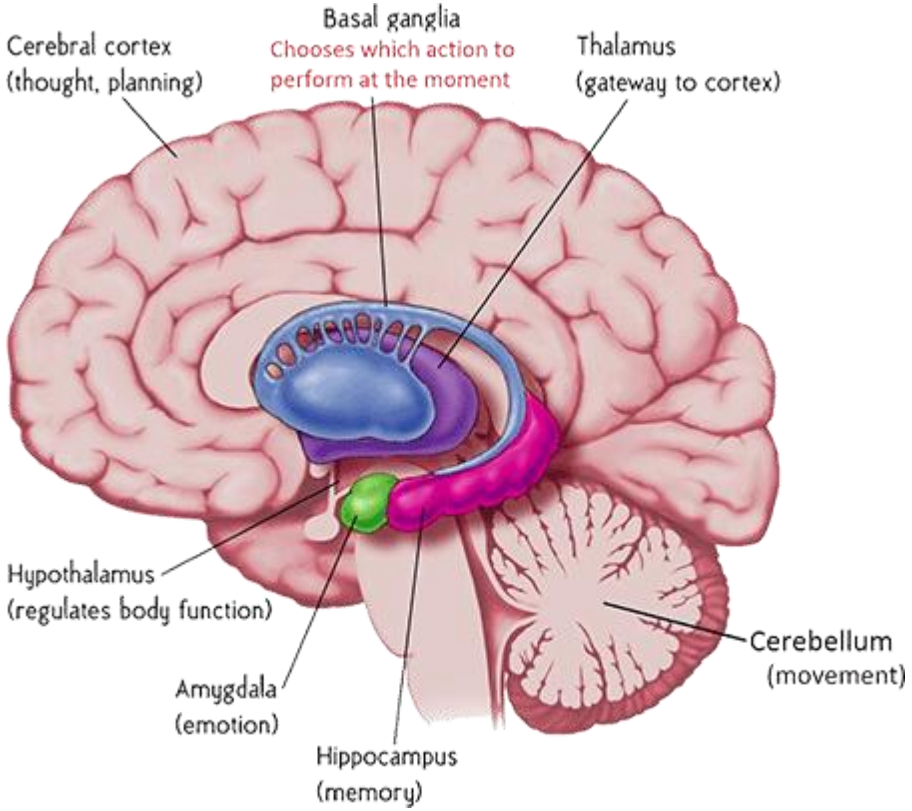
from Doorenweerd et al. (2017), *Scientific reports*

Rol of dystrophin isoforms in the brain



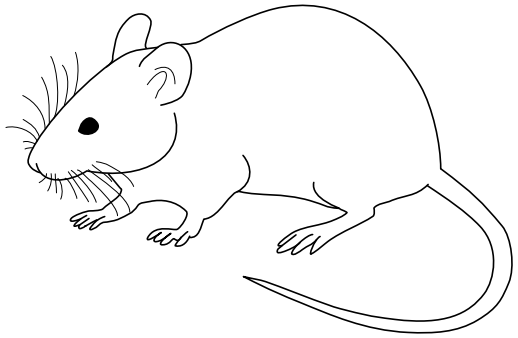
Dp427

- Important for **GABA receptors** (inhibitory brain signals).
- Hypothesis: loss → weaker inhibition in **amygdala & hippocampus** → linked to **anxiety, memory problems, motor and cognitive difficulties**.



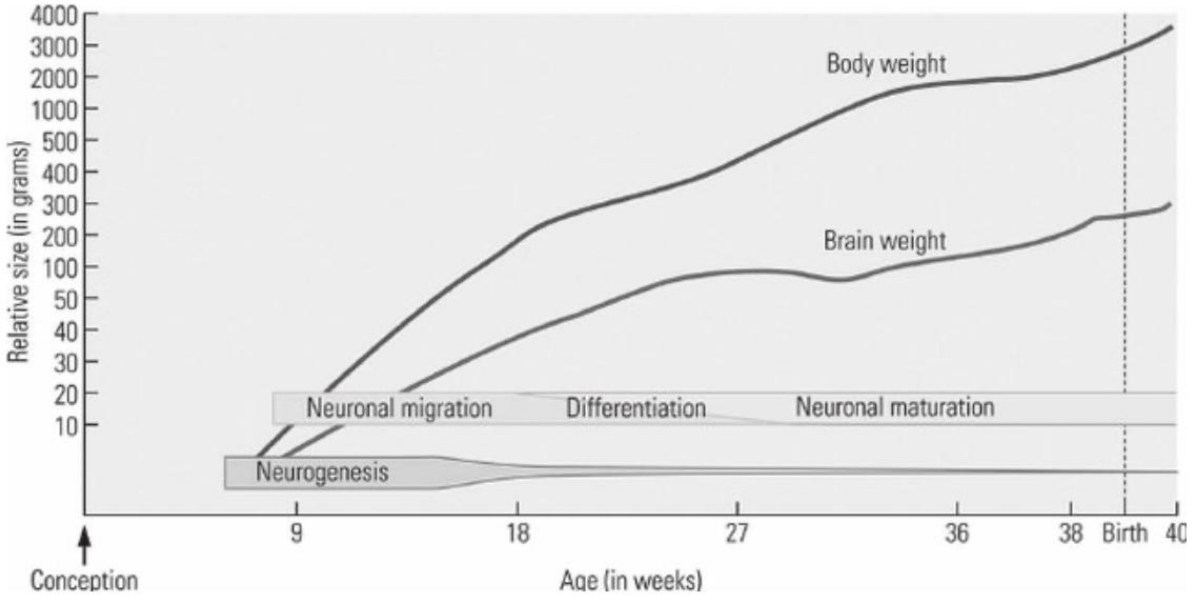
Vaillend, 2025

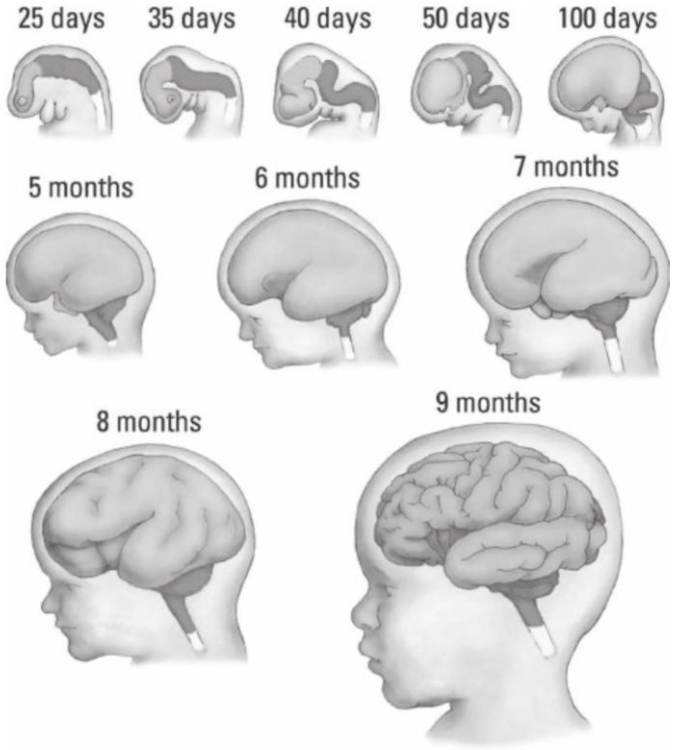
Rol of dystrophin isoforms in the brain



Dp140

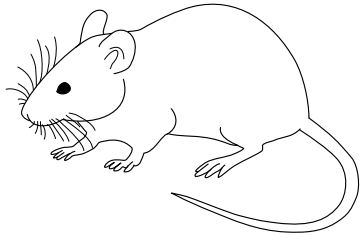
- Active in **early brain development**.
- Hypothesis:
  - Absence (together with Dp427) → **social problems and autism-like features**.
  - Interacts with **calcium channels** → may affect cognitive functions.





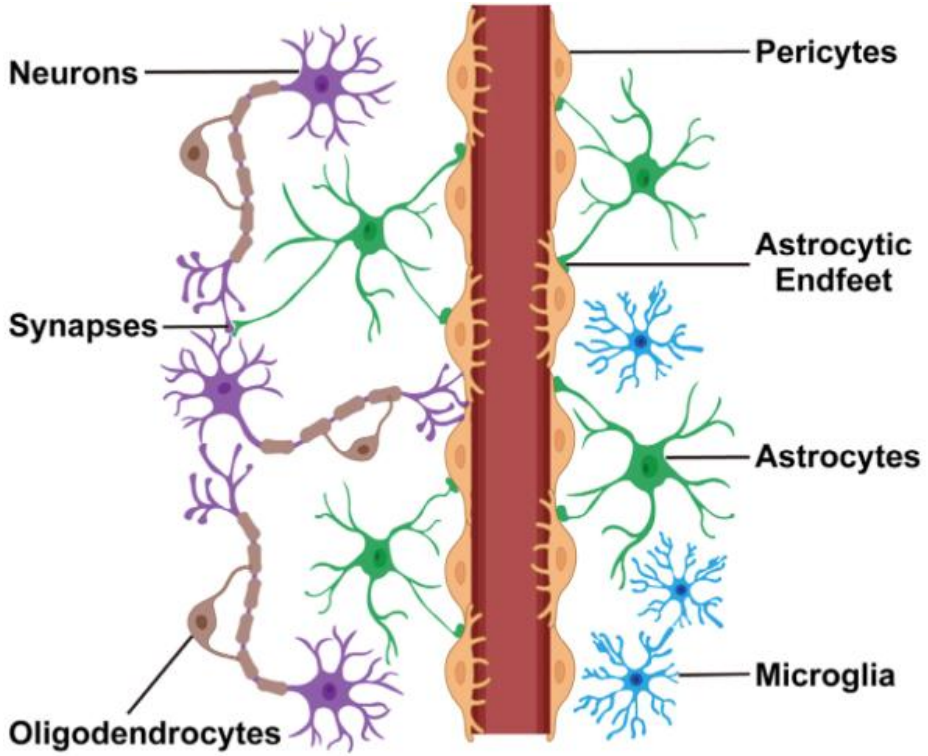
Vaillend, 2025

Rol of dystrophin isoforms in the brain



Dp71

- Most abundant isoform in the brain.
- Crucial for the function of **astrocytes** (supportive brain cells).



Vaillend, 2025

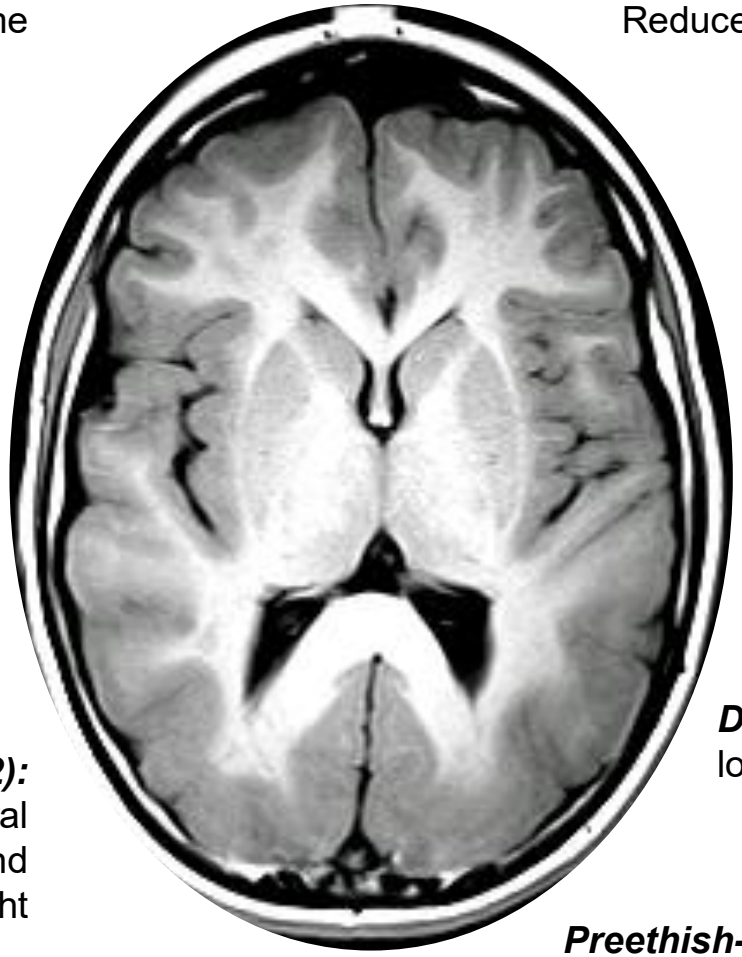
Brain research

Doorenweerd N., et al (2014):
Smaller total brain volume

Doorenweerd N., et al (2014):
Smaller fractional anisotropy (total brain)
Higher mean diffusivity
Higher radial diffusivity

Tracey I., et al (1995):
higher values in brain ratios of inorganic phosphate to adenosine triphosphate, to phosphomonoesters and to phosphocreatine.

Lee J., et al (2002):
Decreased metabolism in 4 clusters (medial temporal structures, cerebellum bilaterally, sensimotor area and lateral temporal cortex on the right



Doorenweerd N., et al (2014):
Reduced grey mass volume

Fu Y., et al (2016):
Reduced FA values in splenium corpus callosum

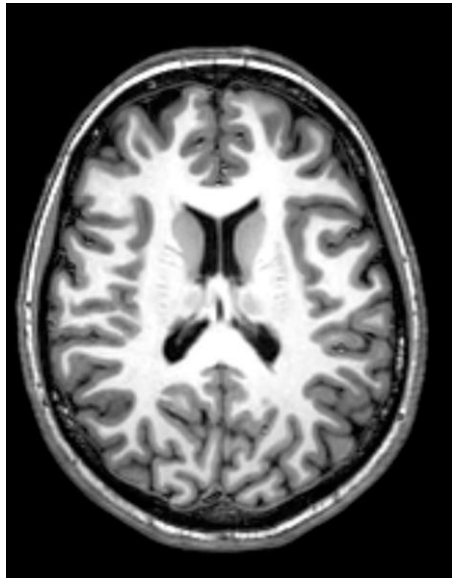
Rae C., et al (1998):
Increase in the ratio of choline-containing compounds to N-acetylaspartate in the left cerebellum

Doorenweerd N., et al (2017): 17% lower cerebral blood flow

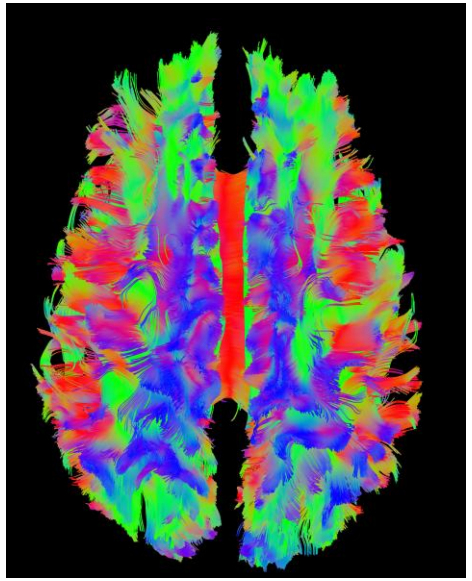
Preethish-Kumar V., et al (2020):
Altered FA values in corpus callosum, parietal WM and fornices

Brain and behaviour

Structure?



Connectivity?



Blood flow?

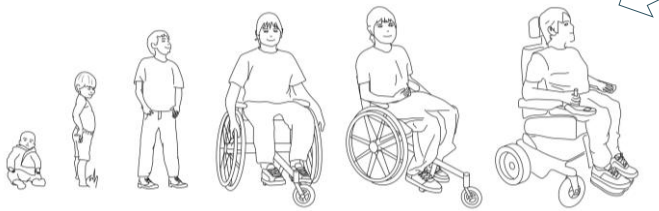
Functioning?

Duchenne muscular dystrophy

dystrophin gene
(X-chromosome)

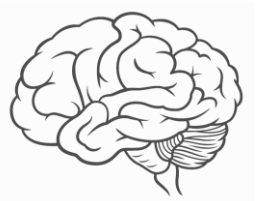
Disrupted production of dystrophin protein

Muscles

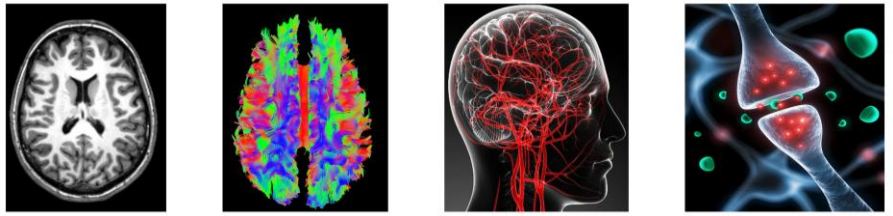


Picture designed by Justus Kuijer

Brain



Structure? Connectivity? Blood flow? Functioning?



- Lower gray matter volume[2]
- Less white matter integrity[2]
- Lower cerebral blood flow[2]

Neurobehavioral difficulties:

- Cognition[1]
- Working memory[1]
- Implicit learning[1]
- Academic learning[1]
- Behavior[1]
- …

[1]Darmahkasih (2020) [2]Doorenweerd

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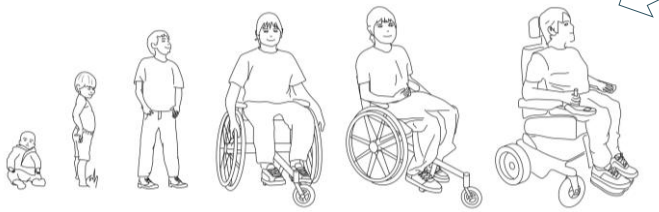

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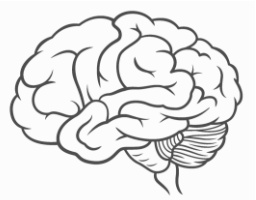
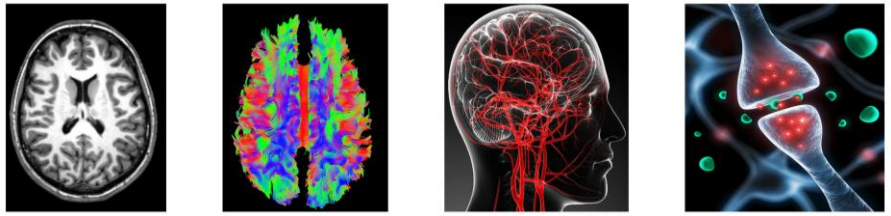
Brain

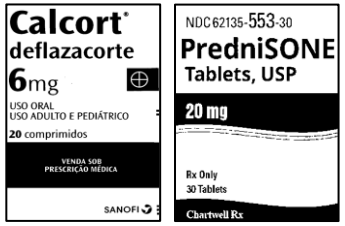


Structure? Connectivity? Blood flow? Functioning?



- Lower gray matter volume
- Less white matter integrity
- Lower cerebral blood flow

Corticosteroids



Daily or Intermittent

?

?

Neurobehavioral difficulties:

- Cognition
- Working memory
- Implicit learning
- Academic learning
- Behavior
- …

[1]Darmahkasih (2020) [2]Doorenweerd

Participants

Controls
n = 40

Scan site Leuven = 20
Scan site Leiden = 20
Mean age = 13.0y ± 2.4

DMDd
n = 20

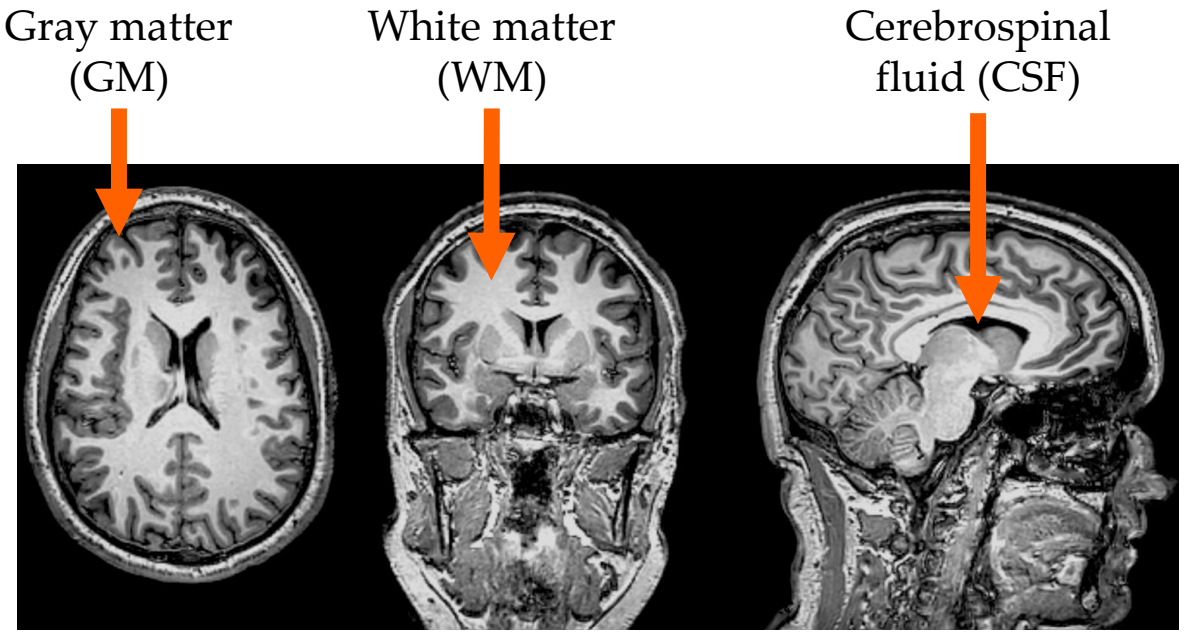
Scan site Leuven = 20
Mean age = 13.2y ± 3.2
Wheelchair bound = 6
CS treatment duration = 81 months

DMDi
n = 20

Scan site Leiden = 20
Mean age = 13.0y ± 3.0
Wheelchair bound = 13
CS treatment duration = 79 months

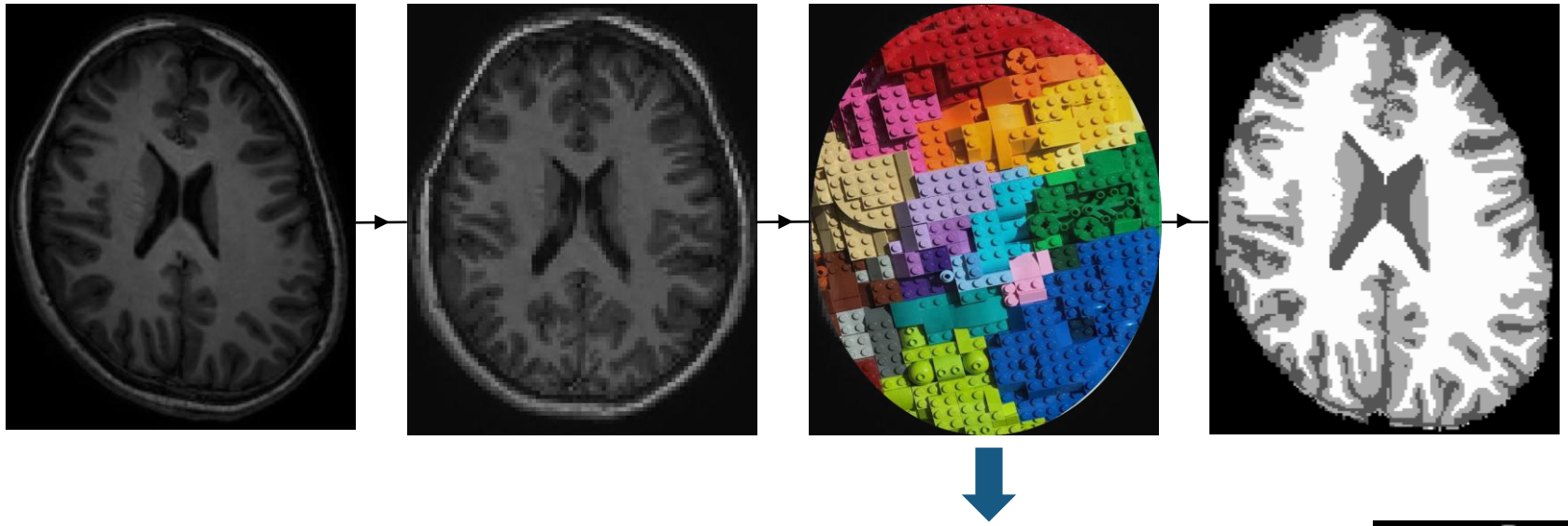
Magnetic Resonance Imaging (MRI)

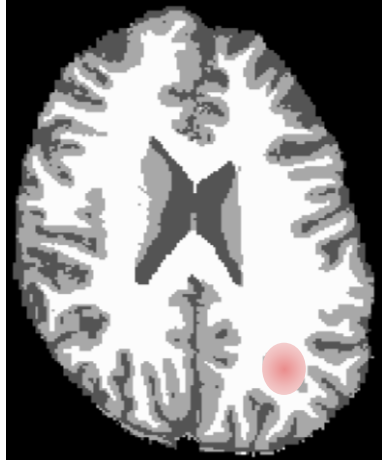
- 2 scan sites: Leuven & Leiden
- 3T Philips Achieva scanner



T1-weighted MR images

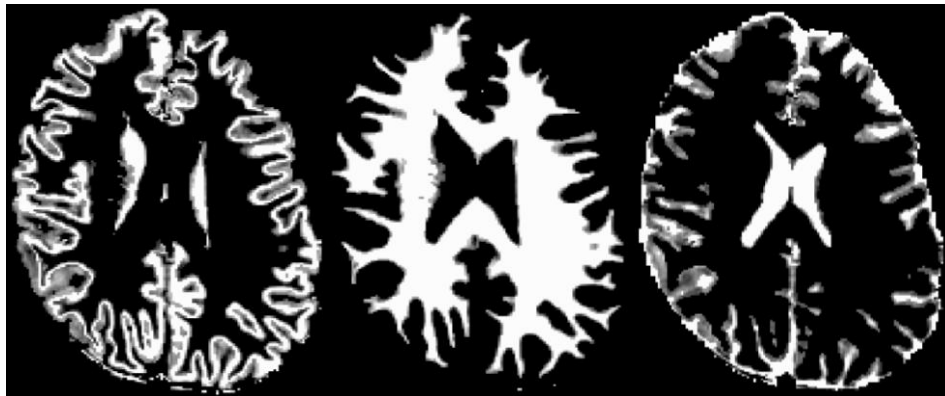
Study 1 | MRI processing





Voxel-based morphometry (VBM)

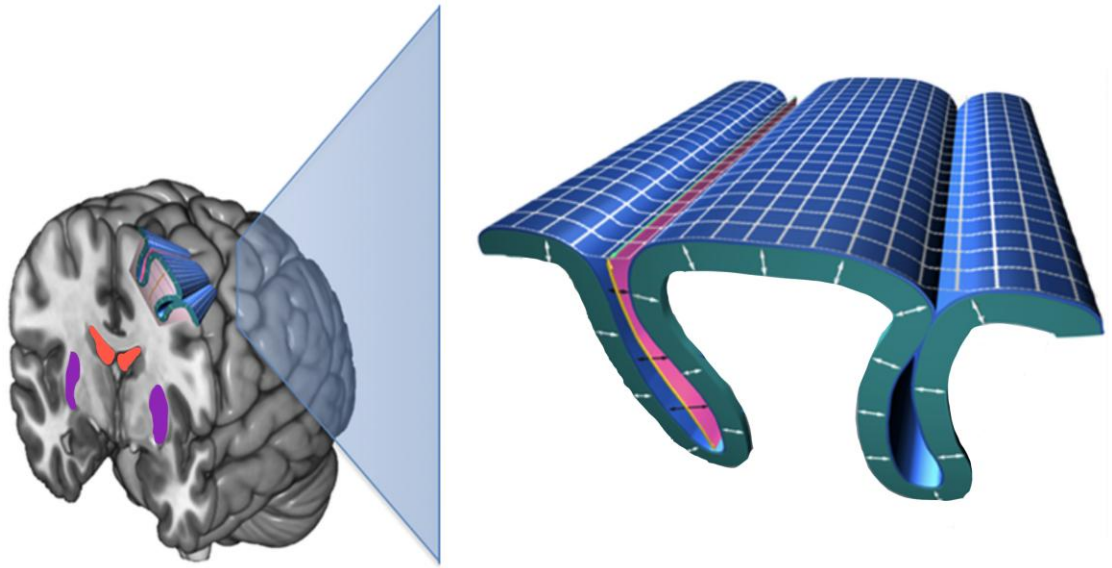
Global GM, WM and CSF volumes



Brain research

Subcortical structures

- Caudate nucleus
- Putamen
- Thalamus
- Amygdala
- Hippocampus
- Cerebellum
- Brain stem
- (Ventricles)

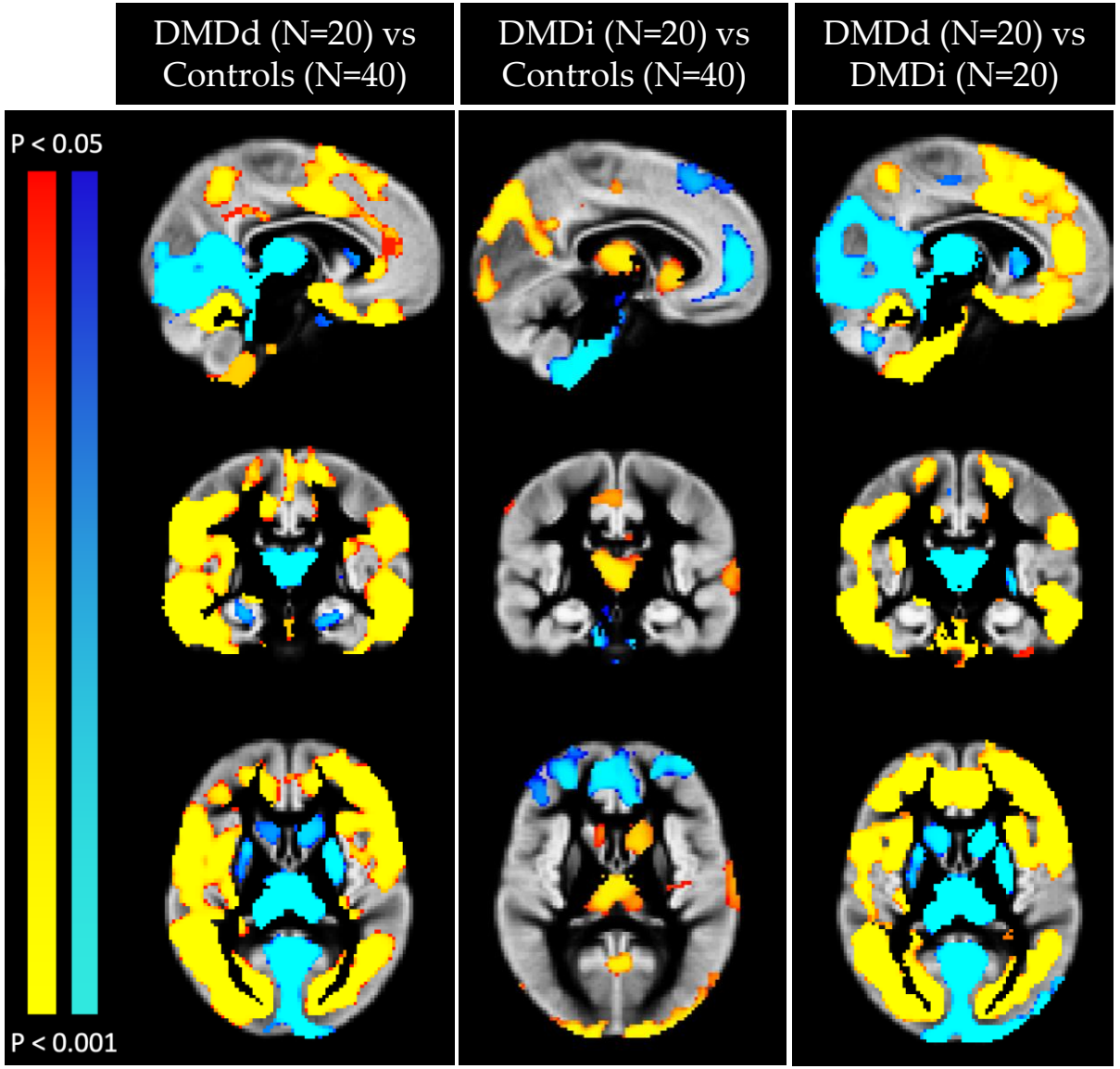


Cortical morphometry:

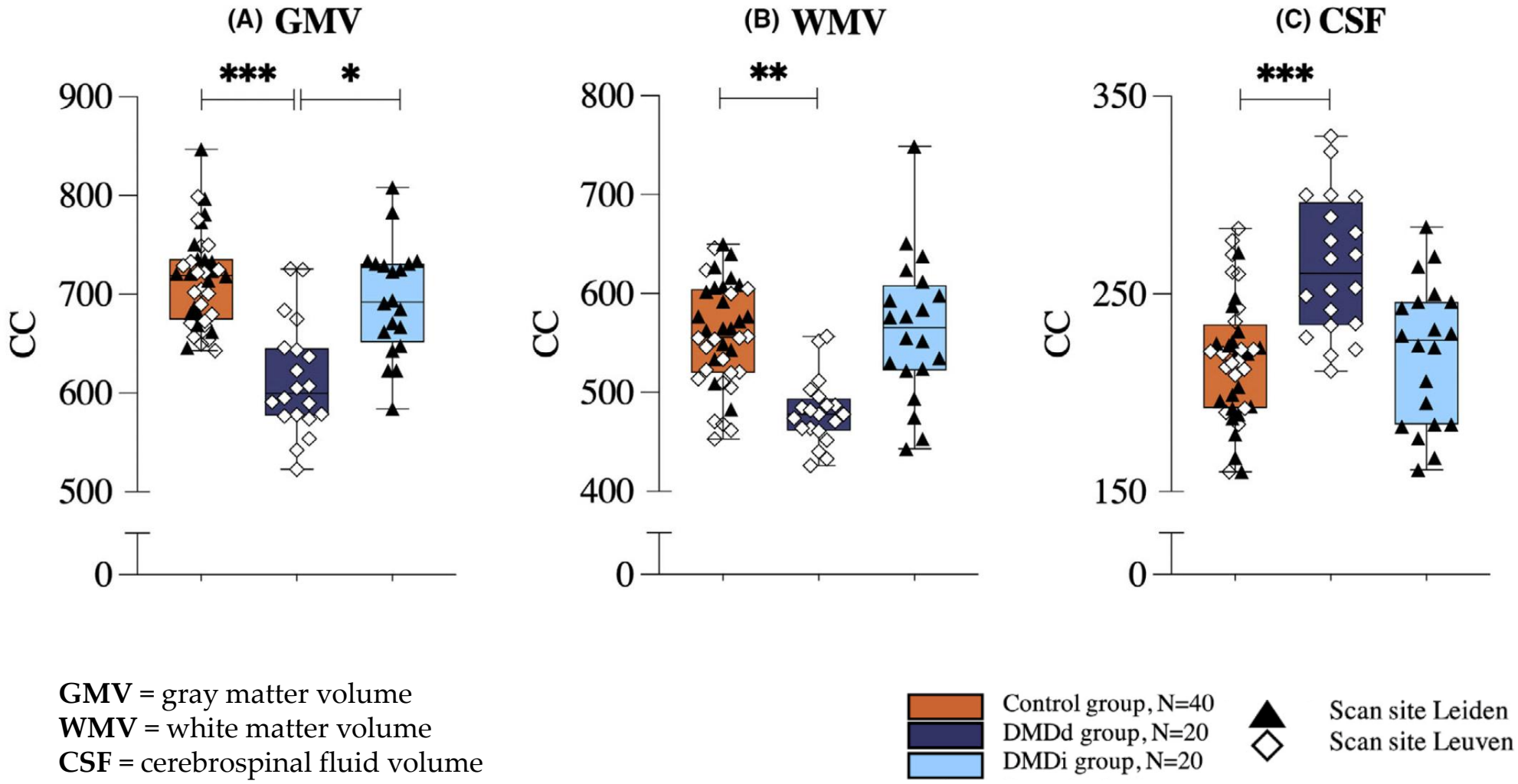
- Cortical thickness
- Sulci depth
- Gyrification index

Figure adapted from Carmona, S. et al. (2019). Pregnancy and adolescence entail similar neuroanatomical adaptations: A comparative analysis of cerebral morphometric changes. Human Brain Mapping. 40. 10.1002/hbm.24513.

Local gray matter concentration



Global brain volumes



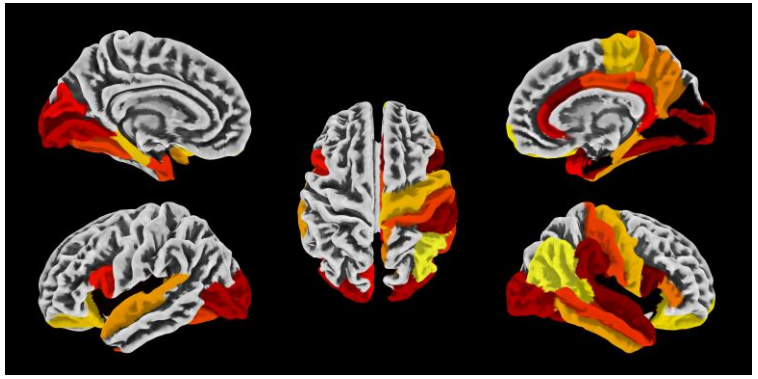
GMV = gray matter volume
WMV = white matter volume
CSF = cerebrospinal fluid volume

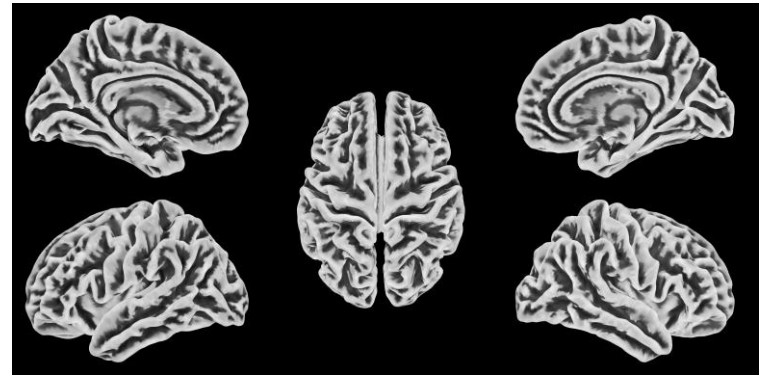
Cortical morphology

Daily versus intermittent

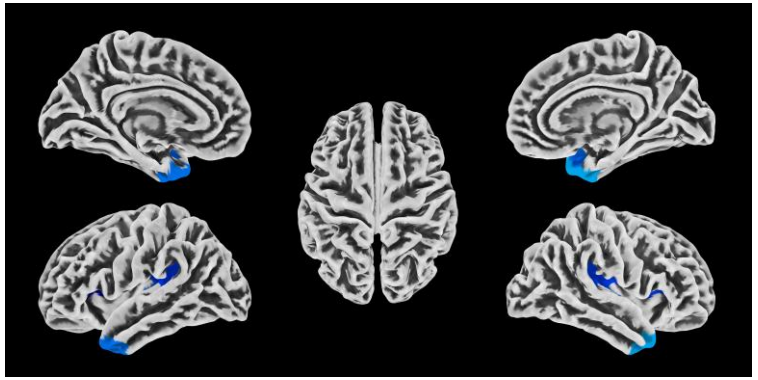
Dp140^{+} versus Dp140^{-}

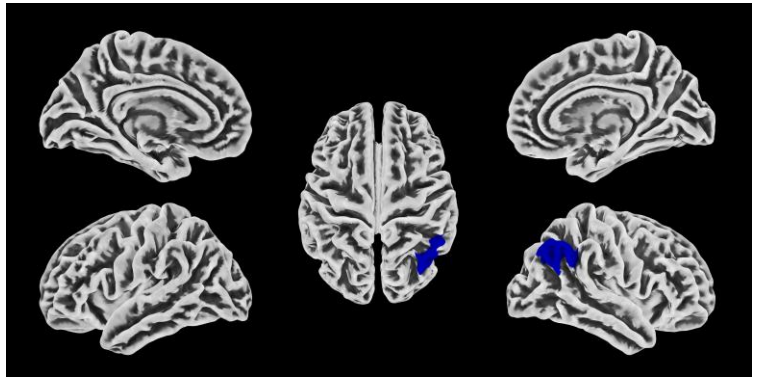
Cortical thickness



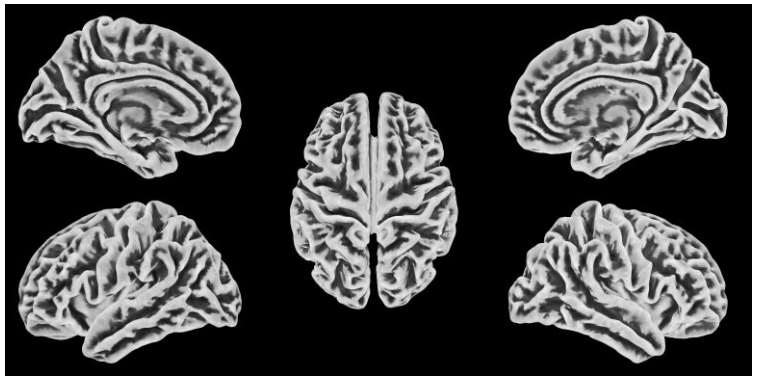


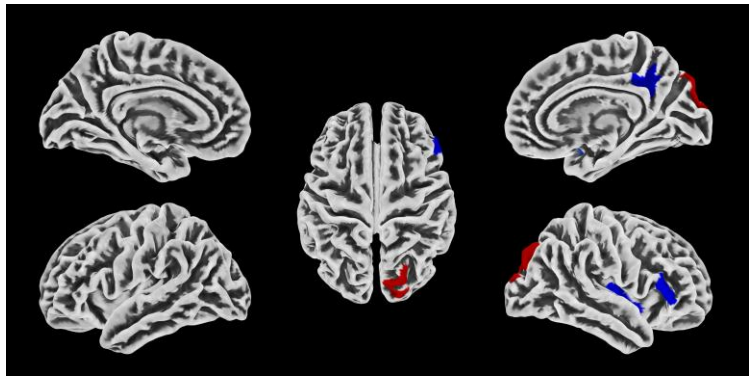
Gyrification index





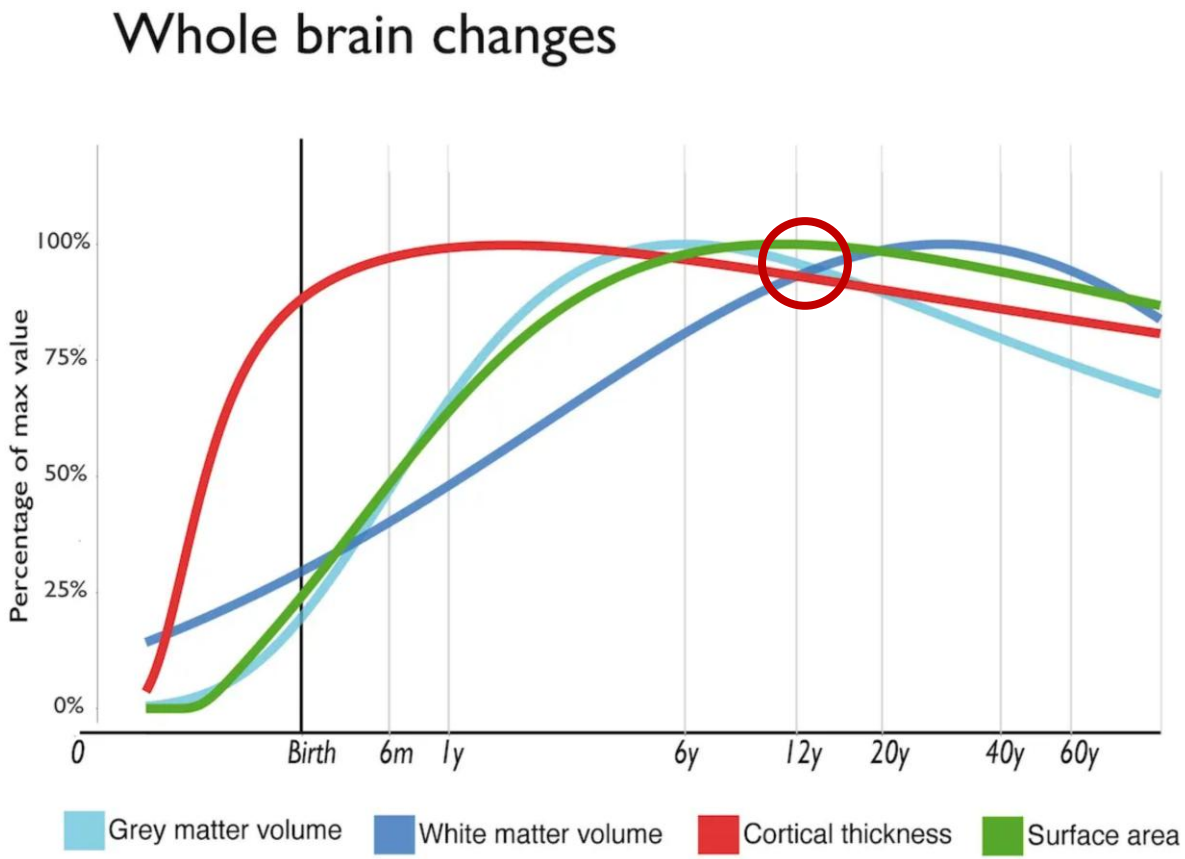
Sulci depth





Corticosteroids conclusion

- Potential difference in interference with cortisol-induced brain maturation processes between corticosteroid regimens (cfr. physical outcomes)



From: Bethlehem, R.A.I., Seidlitz, J., White, S.R. *et al.* Brain charts for the human lifespan.*Nature* **604**, 525–533 (2022).

Corticosteroids conclusion

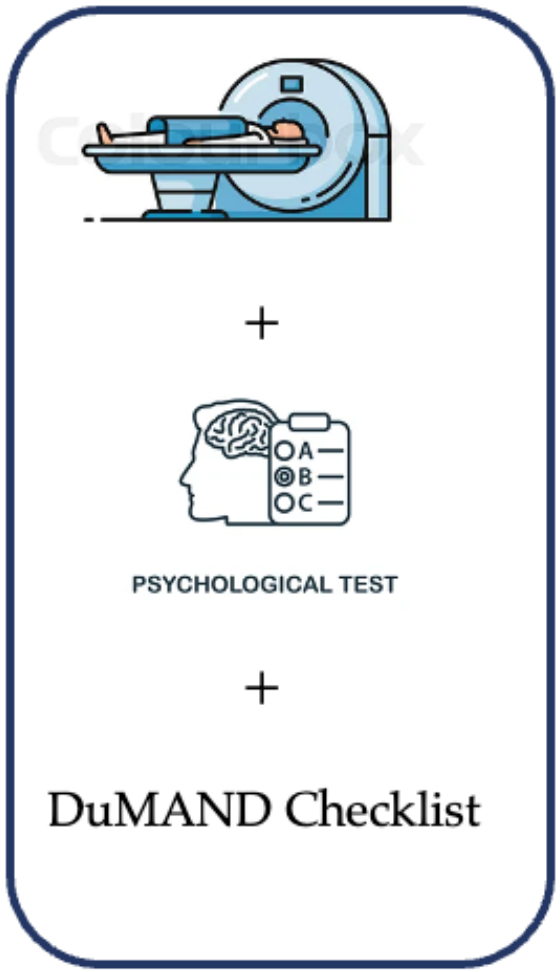
- Potential difference in interference with cortisol-induced brain maturation processes between corticosteroid regimens (cfr. physical outcomes)
- Longitudinal research is needed to chart brain development in patients with DMD
- Future brain research in DMD should consider the potential distinctive impact of both corticosteroids and genotype

Next steps

Leiden University Medical Center

JWMDRC, Newcastle

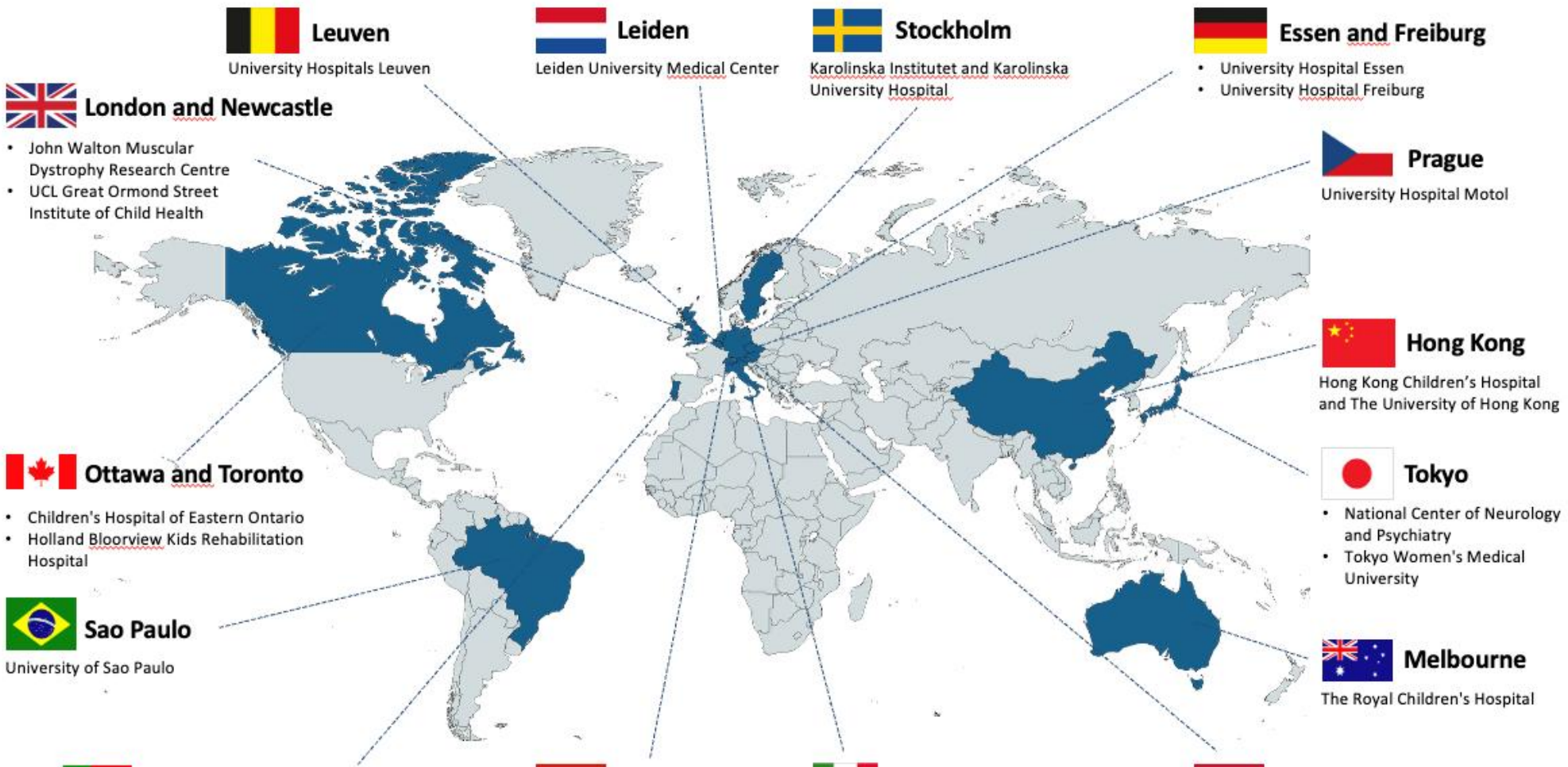
UZ Leuven
KU Leuven



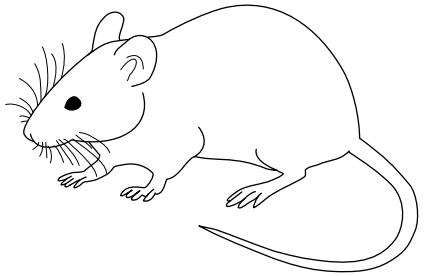
- Prednisolone
- Deflazacort
- Vamorolone

Data processing in Leiden and Leuven

DuMAND Network



What is the goal



Current genetic therapies (Exonskipping, gene therapy) help muscle, but do not cross the blood–brain barrier → brain symptoms of DMD remain untreated.

- Findings in mouse models
  - Dp427 restoration (mdx mice):
    - Direct brain delivery (ICV) of ASOs or viral vectors → partial return of brain dystrophin.
    - Led to reduced anxiety/fear responses and improved memory.
  - Dp427 + Dp140 restoration (mdx52 mice):
    - Exon 51 skipping → restores Dp427 only.
    - Exon 53 skipping → restores both Dp427 and Dp140.
    - Partial restoration improved fear responses, social behaviour, and glutamate signalling.

Hypothesis:

- Postnatal restoration of brain dystrophin can partly reverse cognitive and emotional problems in DMD mouse models.
- Still a large gap before translation to effective human treatments.

UZ LEUVEN

Thanks for your attention

sam.geuens@uzleuven.be