Structural connectivity of dopaminergic nuclei in preterm-born adults

A. Menegaux[1,2], J. Wendt[1,2], B. Schmitz-Koep[1,2], D.M. Hedderich[1,2], M. Daamen[3,4], H. Boecker[3], C. Zimmer[1,2], D. Wolke[5,6], P. Bartmann[4], C. Sorg[1,2,7]

[1]TUM-Neuroimaging Center and departments of [2]Diagnostic and Interventional Neuroradiology, and [7]Psychiatry of Klinikum Rechts der Isar, Technische Universität München TUM
[3]Department of neurology, University Hospital Jena, Departments of [4]Diagnostic and Interventional Radiology and [8]Neonatology, University Hospital Bonn
[5]Department of Psychology and [6]Warwick Medical School, University of Warwick

Klinikum rechts der Isar
Technische Universität München

Contact: aurore.menegaux@tum.de

Technische Universität München

Background

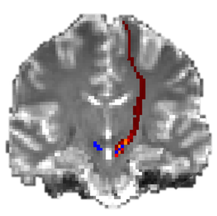
- Preterm birth, (i.e. birth before 37 weeks of gestation) is associated with an altered brain development and a greater risk of cognitive impairments (1).
- The development of the dopaminergic system might be particularly impaired as demonstrated by reduced striatal dopamine synthesis capacity in very preterm born adults with perinatal brain injury (2).
- To study more extensively the dopamine system in human prematurity, we investigated the structural connectivity (SC) of dopaminergic nuclei in a cohort of 63 very preterm or very low birth weight (VP/VLBW) adults and 81 term-born controls aged 26 years using probabilistic tractography.

Material and Methods

Table 1: Sample Characteristics

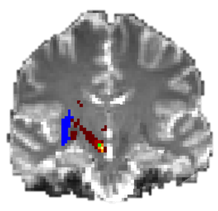
	VP/VLBW (N=63)			FT (N=81)			
	Mean	SD	Range	Mean	SD	Range	p-value
Sex (male/female)	35/28			50/31			0.282
Age (years)	26.8	± 0.6	25.8 – 28.3	26.9	± 0.7	25.6 – 28.9	0.147
GA (weeks)	30.1	± 1.9	25 – 36	39.7	± 1.0	37 – 42	<0.001
BW (g)	1303	± 328	630 – 2070	3376	± 480	2120 – 4670	<0.001
Full-scale IQ[a]	94.3	± 13.0	64 – 131	103.0	± 12.5	77 – 130	<0.001
Verbal IQ[a]	98.9	± 14.0	62 – 137	106.4	± 14.7	79 – 143	0.003
Performance IQ[a]	89.8	± 13.7	56 – 118	98.8	± 10.7	69 – 123	<0.001

A



Example of probabilistic tractography from the left SN (blue) to the left prefrontal cortex

B



Example of probabilistic tractography from the right SN (green) to the right putamen

- Preprocessing with PreQual (4) which included denoising with MRtrix3 (5) and susceptibility-induced distortion, motion and eddy currents correction using FSL top-up and EDDY respectively (6).
- Ventral tegmental area (VTA) and substantia nigra pars compacta (SN) masks generated using the Harvard ascending arousal network atlas (7) and Pauli (8) atlas respectively. Prefrontal, striatum and hippocampi masks created from the Harvard-Oxford atlases (9).
- Probabilistic tractography performed from a combined VTA and SN mask first (referred to as dopa mask) to left and right prefrontal, striatum and hippocampus ROIs. Then from VTA and SN separately. Finally, we subdivided prefrontal and striatal masks into smaller ROIs.
- Structural connectivity was measured two different ways:
  Connection probability (CP) = (total number of streamlines generated from the seed ROI reaching the target ROI / (5000 x number of voxels in the seed ROI))
  Connection Density = (total number of streamlines generated from the seed ROI reaching the target ROI / (volume seed ROI + volume target ROI)
- Group differences in CP and CD analyzed using general linear models.
- To investigate whether group differences in CP were specifically related to birth variables (gestational age (GA), birth weight (BW)) or cognitive performance (IQ scores), we performed two-tailed partial Pearson correlation analyses within the VP/VLBW group.
- Sex and scanner were entered as covariates of no interest in all models. Statistical significance was defined as $p < 0.05$.

Results

1. Group differences in structural connectivity to regions of interest

	Connection Probability			Connection Density		
	Dopa	***VTA***	***SN***	***Dopa***	***VTA***	***SN***
Left PFC	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right PFC	n.s.	n.s.	**4.8|.031**	**6.4|.012**	n.s.	**10.0|.002**
Left Striatum	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right Striatum	**3.1|.007**	n.s.	**5.8|.017**	**7.3|.008**	n.s.	**9.3|.003**
Left Hippocampus	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right Hippocampus	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Results are reported as: F-value | p-value

We found:

- Reduced CP (F= 3.1 p = .007) and CD (F= 7.3, p = .008) between dopa and right striatum in VP/VLBW adults
- Reduced CD (F= 6.4 p = .012) between Dopa and right prefrontal cortex in VP/VLBW adults

Control analyses:

1) Tracking from VTA and left and right SN separately we found
   - Reduced CP (F= 5.8. p = .017) and CD (F= 9.3, p = .003) between SN and right striatum in in VP/VLBW adults
   - Reduced CP (F= 4.8 p = .031) and CD (F= 10.0 p = .002) between SN and right prefrontal cortex in VP/VLBW adults

2) Tracking to finer parcellations of striatum and prefrontal cortices we found
   - Reduced CP (F= 5.7. p = .020) and CD (F= 7.3, p = .008) between dopa and right putamen
   - Reduced CP (F= 6.0. p = .016) and CD (F= 7.5, p = .007) between SN and right putamen
   - Reduced CP from VTA (F = 5.1 p = .02) and reduced CD from SN (F = 4.8 p = .030) to right caudate nucleus
   - Reduced CP (F= 4.6. p = .034; F= 5.8. p = .017) and CD (F= 7.5, p = .008; F= 9.0. p = .003) from dopa and SN to right VL-PFC respectively in VP/VLBW adults.
   - Increased CP fron VTA to right DL-PFC in VP/VLBW adults

No significant associations between connectivity values and GA, BW or IQ variables were found

2. Group differences in structural connectivity to refined prefrontal cortical regions

	Connection Probability			Connection Density		
	Dopa	***VTA***	***SN***	***Dopa***	***VTA***	***SN***
Left DL-PFC	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right DL-PFC	n.s.	**6.5|.012**	n.s.	n.s.	n.s.	n.s.
Left VL-PFC	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right VL-PFC	**4.6|.034**	n.s.	**5.8|.017**	**7.2|.008**	n.s.	**9.0|.003**

Results are reported as: F-value | p-value

3. Group differences in structural connectivity to striatum subnuclei

	Connection Probability			Connection Density		
	Dopa	***VTA***	***SN***	***Dopa***	***VTA***	***SN***
Left Caudate	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right Caudate	n.s.	**5.1|.02**	n.s.	n.s.	n.s.	**4.8|.030**
Left Putamen	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right Putamen	**5.7|0.02**	n.s.	**6.0|.016**	**7.3|.008**	n.s.	**7.5|.007**
Left Ncl Accumbens	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right Ncl Accumbens	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Results are reported as: F-value | p-value

Abbreviations: VP/VLBW: very preterm, very low birthweight; FT, full-term Dopa, dopaminergic nuclei = SN + VTA; VTA, ventral tegmental area; SN, Substantia Nigra pars compacta; PFC, prefrontal cortex; DL-PFC, dorsolateral prefrontal cortex; VL-PFC, ventrolateral prefrontal cortex, Ncl accumbens, nucleus accumbens; N.S., non significant; CP, connection probability; CD, connection density, GA; gestational age; BW, birth weight; IQ, intelligent quotient.

Conclusion / Outlook

- Our results seem to suggest some lasting alterations in the structural connectivity of dopaminergic nuclei to the right prefrontal cortex and striatum in preterm born adults.
- No significant associations between SC of SN/VTA and GA/BW were found but SC of dopaminergic nuclei might be more related to the degree of neonatal complications or intraventricular hemorrhage.
- Although we subdivided the prefrontal cortex into ventrolateral and dorsolateral prefrontal cortices, a finer parcellation of the Prefrontal cortices might be of use (such as with orbito-frontal cortices and inferior frontal gyri).
- No significant association of SC with full-scale IQ nor IQ subscores were found and it might be relevant to investigate its link to participants' psychiatric state instead using the Pliksi or YASR scores.

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