

# Cognitive Networks of Young-Onset and Late-Onset Alzheimer's Disease Dementia

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## Background

- In young-onset Alzheimer's disease (YOAD), dementia symptom onset is before the age of 65, in contrast to late-onset Alzheimer's disease (LOAD).<sup>1</sup>
- YOAD can present with different cognitive profiles compared to LOAD.
  - YOAD presents more often non-amnestic compared to LOAD, with frequent executive, language and visuospatial presentations.<sup>2,3</sup>
- Exploring interactions between cognitive functions in both YOAD and LOAD can uncover more of their specific cognitive symptomatology and differences between YOAD and LOAD can be identified and tested.<sup>4,5</sup>
- Psychometric network analysis is a technique to<sup>6,7,8</sup>:
  1. Detect **unique differences** in cognition between groups
  2. Identify **key cognitive symptoms**
  3. Reveal **interactions** between cognitive functions and domains
  4. Discover important **neuropsychological instruments** for diagnostics

## Highlights

- The **cognitive symptomatology** of YOAD and LOAD was explored with **psychometric network analysis** and is presented in the **networks** below.
- As expected, **verbal episodic memory** reflects a key symptom in LOAD. In YOAD, however, **associative memory** and **cognitive flexibility** appear more influential.

## Results

- In the YOAD and LOAD network, respectively 48 and 50 edges out of 171 edges were present.
- The networks were found to differ in node-strength centrality:
  - VAT B,  $p=.044$ , is more central in the YOAD network.
  - TMT B,  $p=.044$ , is more central in the YOAD network.
  - RAVLT delayed recall,  $p=.017$ , is more central in the LOAD network.
- The networks did not differ in overall connectivity,  $S=0.59$ ,  $p=.538$ .
- Nor did the networks differ in network structure,  $M=0.38$ ,  $p=.073$ .
- Visually, semantic fluency appears to be a central task in both networks.
- There are connections both within and between cognitive domains.

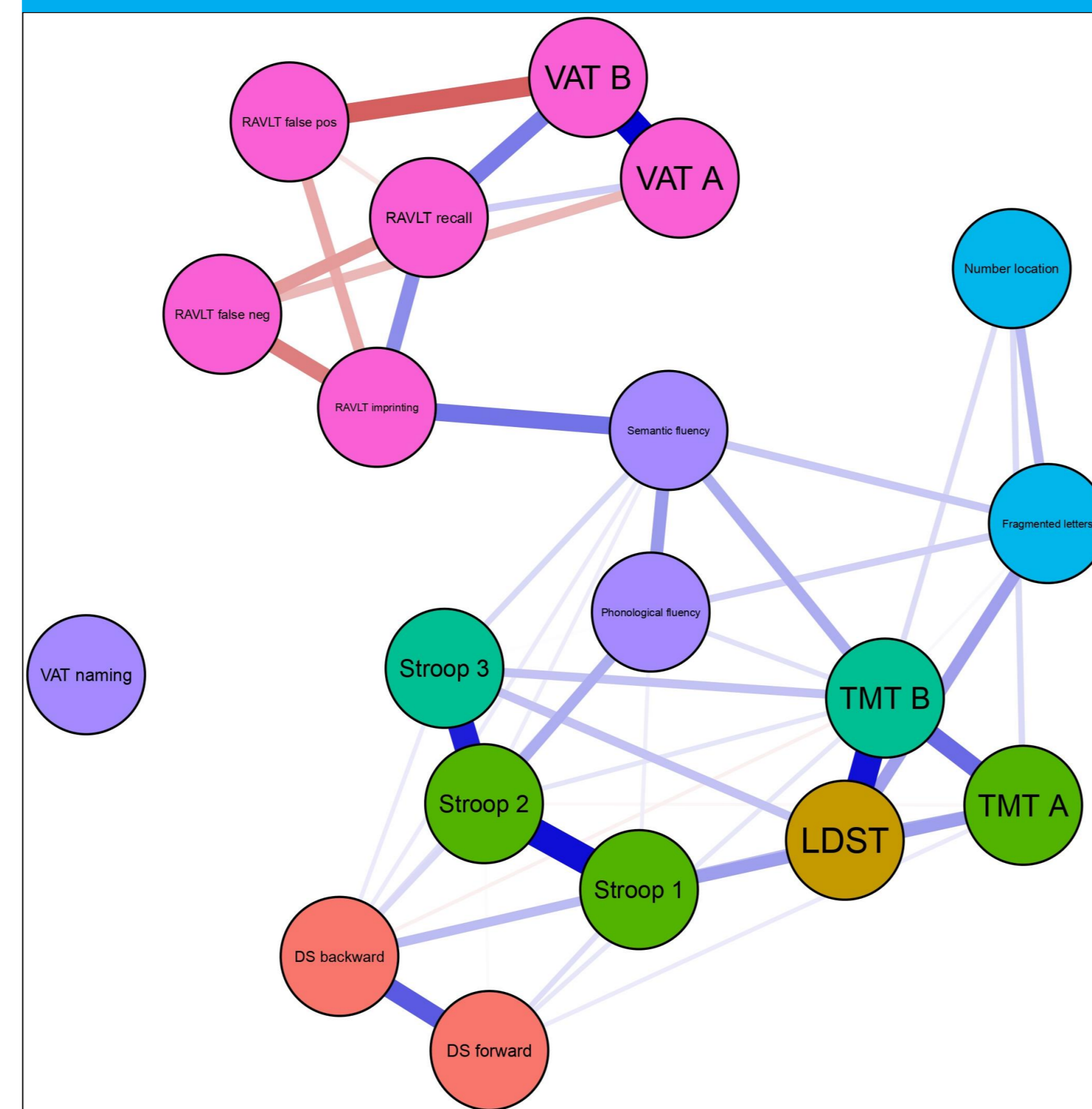
## Methods

- Patients with Alzheimer's disease dementia who had a neuropsychological assessment available were included from the Amsterdam Dementia Cohort.

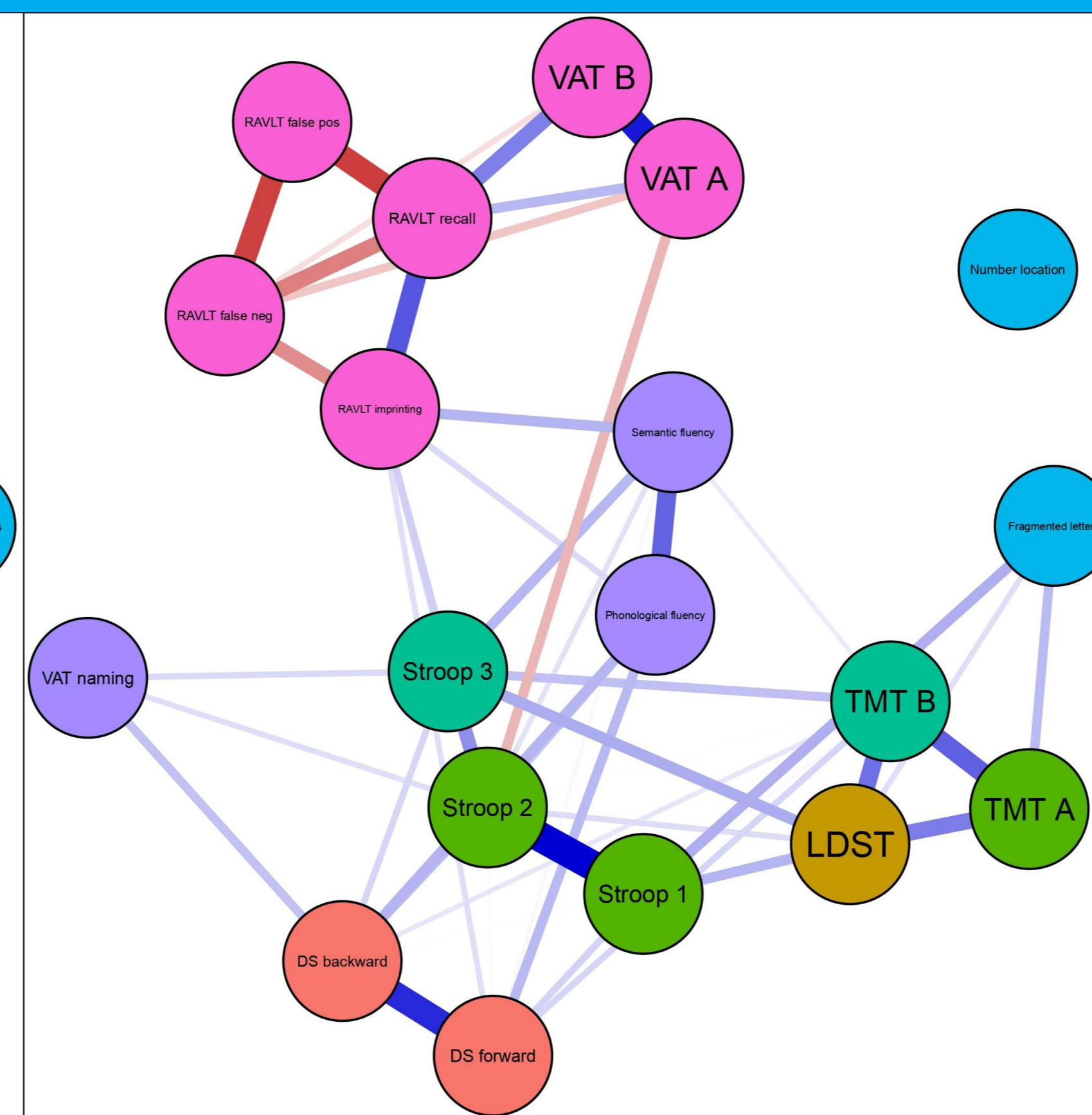
	YOAD (≤65)	LOAD (>65)	P-value	
N	146	193		
Age	59.17±5.15	71.18±3.67	<.001	
Sex (female)	64 (43.8%)	78 (40.4%)	.602	
Education (Verhage)	Did not complete college			
	1	0 (0.0%)	2 (1.0%)	.045
	2	1 (0.7%)	2 (1.0%)	
	3	5 (3.4%)	14 (7.3%)	
	4	22 (15.1%)	48 (24.9%)	
	5	36 (24.7%)	49 (25.4%)	
	Completed college			
6	57 (39.0%)	49 (25.4%)		
7	25 (17.1%)	29 (15.0%)		
MMSE	23.68±3.10	24.07±3.01	.254	

- Two regularized pairwise Gaussian graphical models were estimated with EBIClasso ( $\gamma=0.5$ , Spearman correlations)<sup>9,10</sup>, each including nineteen cognitive (sub)tests (table 1) corrected for age, sex and education.
- Differences between the networks were tested using Network Comparison Tests for global network structure, global strength and centrality (node strength, node betweenness and node closeness).<sup>8</sup>

## YOAD

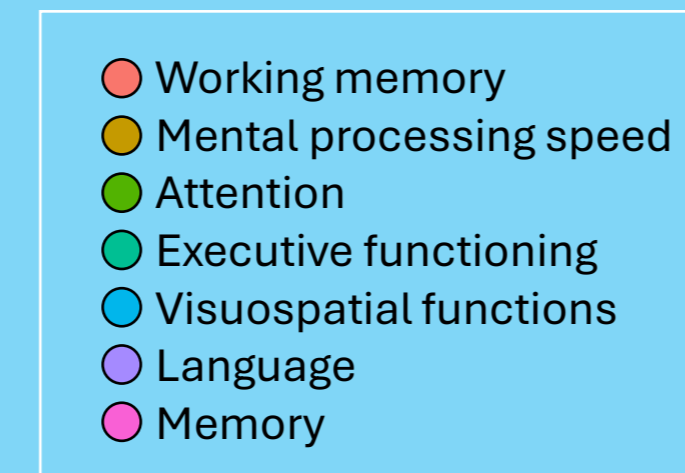


## LOAD



## Legend

Nodes represent cognitive (sub)tests. The colour of each node indicates its cognitive domain.



Edges represent associations. Thicker and darker edges indicate stronger associations.

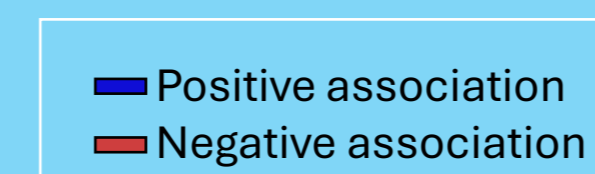


Table 1: Cognitive (sub)tests included in the networks

Node	Definition
RAVLT imprinting	Sum of trials 1-5 of the Rey Auditory Verbal Learning Test
RAVLT recall	Delayed recall of Rey Auditory Verbal Learning Test
RAVLT false positives	False positives in recognition of Rey Auditory Verbal Learning Test
RAVLT false negatives	False negatives in recognition of Rey Auditory Verbal Learning Test
VAT A	Visual Association Test part A
VAT B	Visual Association Test part B
VAT naming	Naming of items in VAT A
Semantic Fluency	Animal fluency
Phonological fluency	Letter fluency total score of 3 letters
Number location	Subtest of Visual Object and Space Perception battery
Fragmented letters	Subtest of Visual Object and Space Perception battery
TMT A	Trail Making Test part A
TMT B	Trail Making Test part B
Stroop 1	Stroop Colour-Word Test word reading
Stroop 2	Stroop Colour-Word Test colour naming
Stroop 3	Stroop Colour-Word Test colour-word
DS forward	Digit span forward
DS backward	Digit span backward
LDST	Letter Digit Substitution Test

## Discussion

- Network analysis reveals unique relationships among cognitive functions which were found to differ between YOAD and LOAD.
- Three tasks appear to reflect key symptoms that differ between YOAD and LOAD in the overall cognitive symptomatology:
  1. **Associative memory** (VAT B) is more pronounced in YOAD
  2. **Cognitive flexibility** (TMT B) is more pronounced in YOAD
  3. **Verbal episodic memory retrieval** (RAVLT delayed recall) is more pronounced in LOAD
- In LOAD, episodic memory retrieval is as expected found to be a key symptom<sup>11,12</sup>, but associative memory and executive functioning<sup>13</sup> are overall more prominent in YOAD.
- Network analyses provide opportunities for generating hypotheses and pave the way for confirmatory research.

References: <sup>1</sup>Van de Veen et al. (2022), <sup>2</sup>Koedam et al. (2010), <sup>3</sup>Sarto et al. (2022), <sup>4</sup>Borsboom et al. (2022), <sup>5</sup>Ferguson & Alzheimer's Disease Neuroimaging Initiative (2021), <sup>6</sup>Epskamp et al. (2018), <sup>7</sup>Epskamp et al. (2022), <sup>8</sup>Van Borkulo et al. (2022), <sup>9</sup>Blanken et al. (2022), <sup>10</sup>Isvoranu & Epskamp (2021), <sup>11</sup>Joubert et al. (2016), <sup>12</sup>McKhann et al. (2011), <sup>13</sup>Tort-Merino et al. (2022) Email: m.a.b.j.van.de.glind@umcg.nl