DELPHI (Direct Non-invasive Brain Network Electrophysiology) For the Evaluation of Brain Health

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DUTCH ISRAELI MINI-SYMPOSIUM ON AI AND DEMENTIA

רמב״ם מרכז רפואי
אקדמי מצטיין
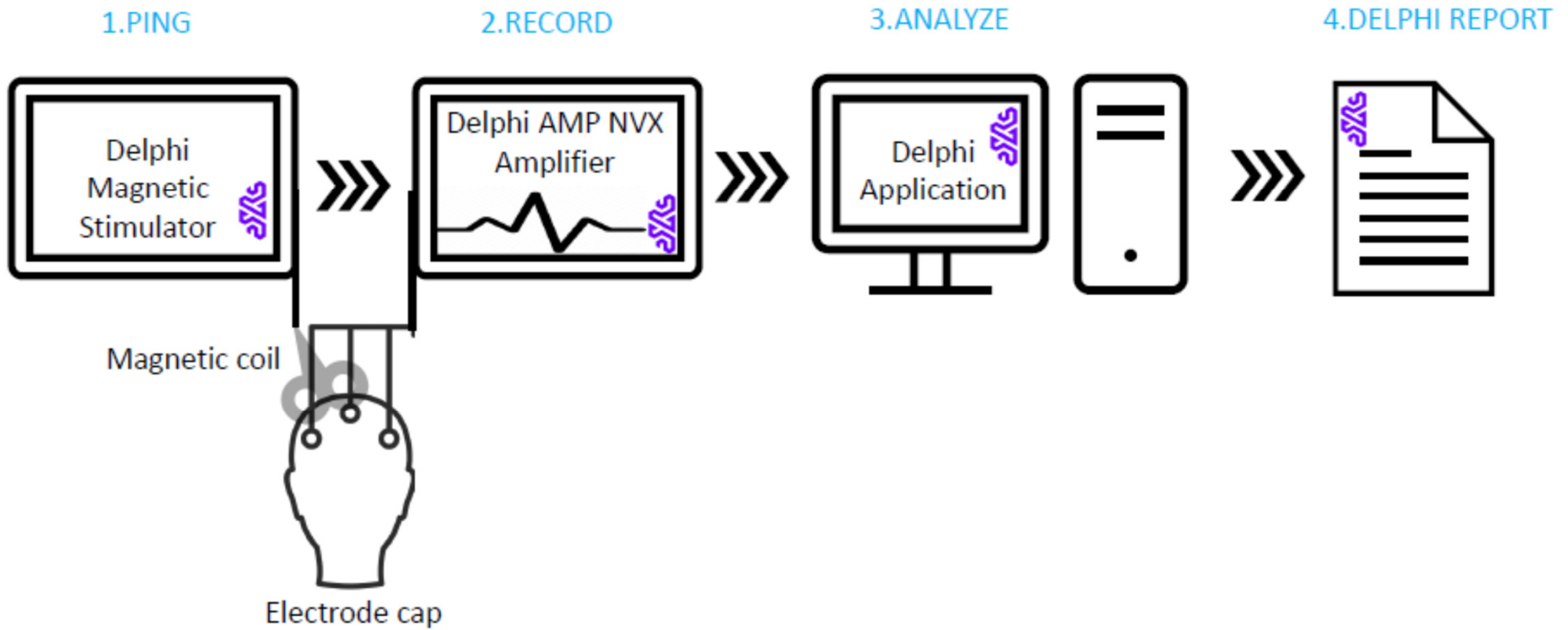
רמב״ם
הקריה הרפואית לבריאות האדם

Functional - *DELPHI direct electrophysiological imaging*


TMS Evoked-Potentials (TEPS)

Non-invasively probes brain function with focused magnetic stimulation and electrophysiological recordings providing reliable, objective, and quantifiable information related to excitation, inhibition, oscillatory neuronal activity, connectivity, and plasticity

1. Place electrode cap (fit to head size)

2. Measure patients motor threshold (MT) for left and right hands—the minimal magnetic stimulation intensity required to invoke a hand muscle twitch.

3. Evaluate brain response for left and right cortical stimulation (automatically performed by Delphi system)

4. Automatic generation of output report

1.PING

2.RECORD

3.ANALYZE

4.DELPHI REPORT

Delphi Magnetic Stimulator

Delphi AMP NVX Amplifier

Delphi Application
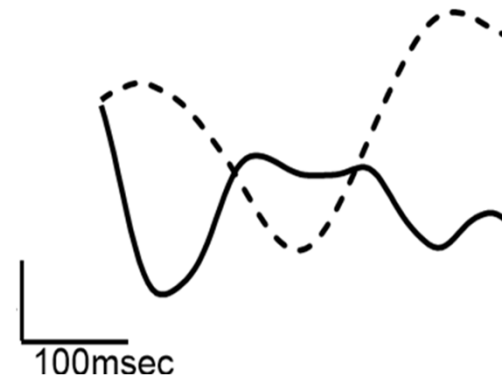
Magnetic coil

Electrode cap

MARGNETICALY INDUCED NETWORK RESPONSE

DELPHI's magnetically induces brain response is the brain's physiological signature,

much like a cardiac 'ECG' with specific amplitudes and latencies for normal brain response

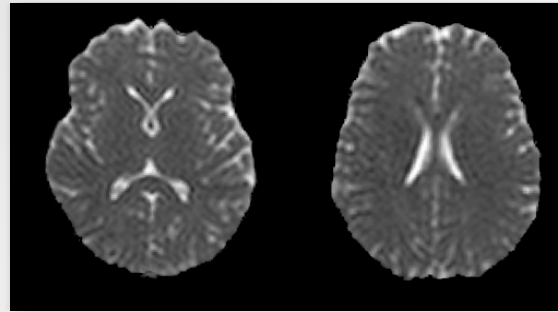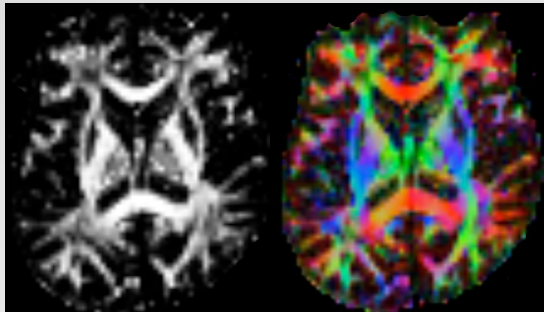1. Example of a Normal response
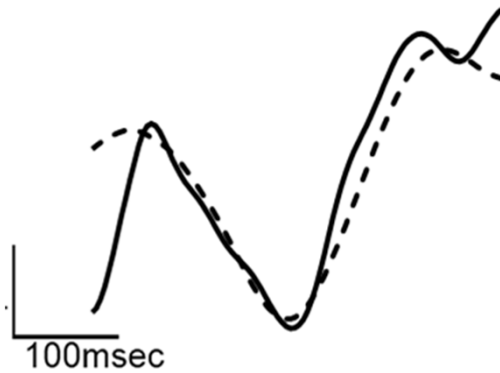
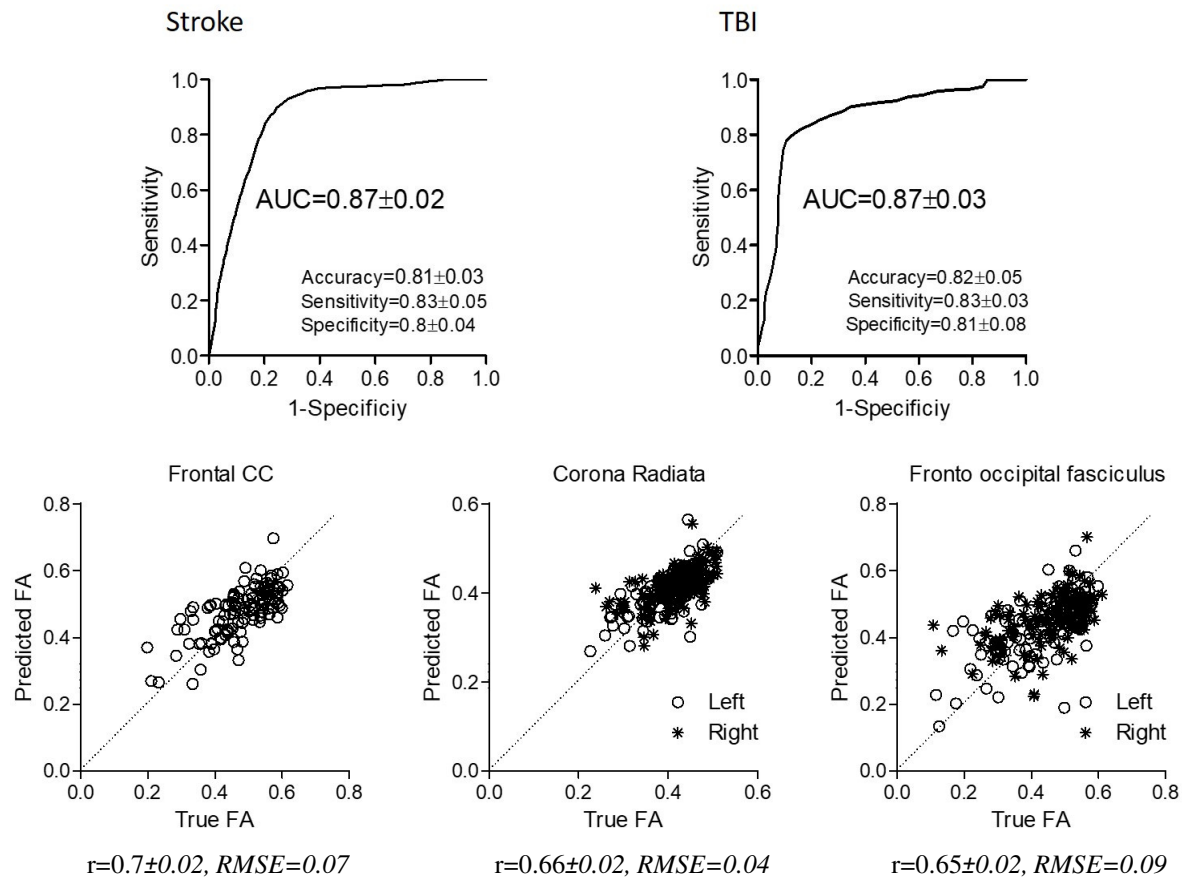2. Example of an Abnormal response

DELPHI OUTPUT MEASURES

DELPHI output measure	Measure	Range	Meaning
Wave Form Adherence (WFA)	Total brain response adherence score to normal response	-1<WFA<1 1 = perfectly normal response compared to age related norm	Indicates network connectivity, white matter integrity and functionality in transmitting the electrical response.
Area Under the Curve (AUC)	Total amplitude of brain response	> 0	Indicates brain excitability. Decreases with age.
Short Term Plasticity (STP)	Short term plasticity : Ability of the network to reflect changes in the ration between Excitation/ Inhibition	-1<STP<1	Indicates white matter integrity in inter-hemispheric tracts (transcallosal fibers-Corpus Collosum)

Structural DTI: local Tensor Derived Measures

- **Fracional anisotropy (FA)** (ellipsoid eccentricity): degree of anisotropy in a given voxel. FA is greater in white matter and smallest in unorganized brain tissue *index of white matter integrity*.

- **Mean diffusivity (MD)** (average ellipsoid size): rotationally invariant magnitude of water diffusion (trace/3). MD is largest in CSF and smallest in organized white matter *reflects brain tissue atrophy and pathology*

Evaluation of White Matter Integrity Utilizing DELPHI™ (TMS-EEG) System

Stroke — AUC=0.87±0.02, Accuracy=0.81±0.03, Sensitivity=0.83±0.05, Specificiy=0.8±0.04

TBI — AUC=0.87±0.03, Accuracy=0.82±0.05, Sensitivity=0.83±0.03, Specificity=0.81±0.08

Frontal CC — r=0.7±0.02, RMSE=0.07

Corona Radiata — r=0.66±0.02, RMSE=0.04

Fronto occipital fasciculus — r=0.65±0.02, RMSE=0.09

Levy Lamdan et al. Frontiers in Neuroscience; Dec 2020

INDICATION FOR USE:

The DELPHI System is indicated for use in patients suspected of cognitive impairments that can progress to stroke or dementia. The DELPHI System measures transcranial magnetic stimulation evoked potentials (TEPs) to aid in identifying the presence of structural or functional brain deficits that are indicative of progression to stroke or dementia. The DELPHI System should be used by qualified personnel (physicians, nurses or health care providers) and may be used in physician office, clinic or other medical facility or institution.

FDA

Granted Breakthrough
Designation Medical Device

Study population

Group 1- Healthy (HC)
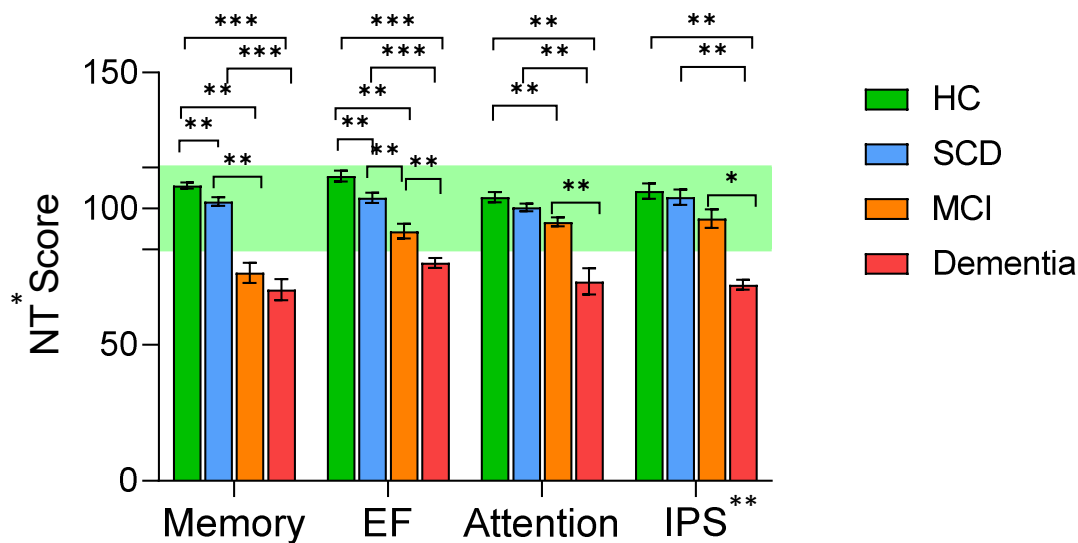Group 2- Subjective Cognitive Decline (SCD)
Group 3- Amnestic Mild Cognitive Impairment (aMCI)
Group 4- Dementia

	HC	SCD	aMCI	Dementia
N	15	17	12	11
Female	6	4	5	4
Male	9	13	7	7
Left-handed	none	2	none	none
Age	66±6	68.6±8.8	68±6	70.1±4
Rest Motor - Threshold	47 ±8	47.7±10	52±10	50±10

Cognitive- *Computerized cognitive testing (Neurotrax)*

		HC	SCD	MCI	Dementia
Memory	Mean	108.4	102.6	76.4	70.2
	SEM	4.4	6.5	12.8	13.0
EF	Mean	111.9	103.9	91.7	80.0
	SEM	7.7	7.7	9.4	6.0
Attention	Mean	104.2	100.4	95.1	73.2
	SEM	7.4	5.9	5.9	15.8
IPS	Mean	106.4	104.2	96.3	72.0
	SEM	10.8	12.1	11.8	6.1

* NT score normalized to age related healthy norms
** IPS – Information Processing Speed

SCD group displayed reduced cognitive performance compared to HC but remained well within normal performance range, aMCI displayed abnormal memory performance and dementia group displayed abnormal performance in all cognitive domains

Front. Neurol., 2021; https://doi.org/10.3389/fneur.2021.699014

Structural MRI: *T1 Gray Matter volume*

T1	HC vs. SCD	HC vs. MCI	HC vs. Dementia	SCD vs. MCI	SCD vs. Dementia	MCI vs. Dementia
Frontal Inferior\Orbital R	0.33	0.19	0.01	0.58	0.04	0.22
Frontal Inferior \Orbital L	0.26	0.29	0.01	0.87	0.08	0.20
Insula Right	0.26	0.03	0.00	0.19	0.02	0.47
Insula Left	0.28	0.13	0.01	0.49	0.05	0.32
Hippocampus Right	0.91	0.06	0.00	0.05	<0.0001	0.10
Hippocampus Left	0.88	0.03	<0.0001	0.03	<0.0001	0.11
Parietal Right	0.87	0.30	0.01	0.32	0.01	0.19
Parietal Left	0.90	0.36	0.01	0.38	0.01	0.15
Temporal Right	0.74	0.11	0.01	0.16	0.01	0.42
Temporal Left	0.70	0.16	0.02	0.24	0.03	0.44

SCD group displayed no change in GM volume, aMCI group displayed significant volume loss in left hippocampus compared to HC and SCD. Dementia subjects displayed significant GM volume loss compared to SCD and HC in most areas but not compared to aMCI

MRI DTI: *White matter fibers fractional anisotropy (FA)*

| DTI-FA p value	HC vs. SCD	HC vs. MCI	HC vs. Dementia	SCD vs. MCI	SCD vs. Dementia	MCI vs. Dementia
Genu of corpus callosum'	0.01	0.02	0.00	0.96	0.31	0.42
Body of corpus callosum'	0.01	0.04	0.00	0.99	0.30	0.39
Splenium of corpus callosum'	0.01	0.07	0.00	0.87	0.08	0.12
Anterior corona radiata L'	0.04	0.02	0.06	0.54	0.97	0.60
Anterior corona radiata R'	0.02	0.02	0.03	0.57	0.84	0.73
Superior corona radiata L'	0.13	0.24	0.40	0.97	0.62	0.70
Superior corona radiata R'	0.17	0.23	0.28	0.91	0.91	0.84
Cingulum (hippocampus) L'	0.05	0.03	0.03	0.53	0.63	0.87
Cingulum (hippocampus) R'	0.04	0.07	0.26	0.82	0.51	0.45
Fornix L'	0.13	0.07	0.02	0.54	0.29	0.75
Fornix R'	0.07	0.03	0.10	0.42	0.96	0.50
Superior longitudinal fasciculus L'	0.01	0.02	0.03	0.68	0.97	0.69
Superior longitudinal fasciculus R'	0.02	0.01	0.03	0.54	0.91	0.65
Superior fronto-occipital L'	0.00	0.04	0.00	0.41	0.98	0.48
Superior fronto-occipital R'	0.00	0.01	0.00	0.91	0.33	0.48
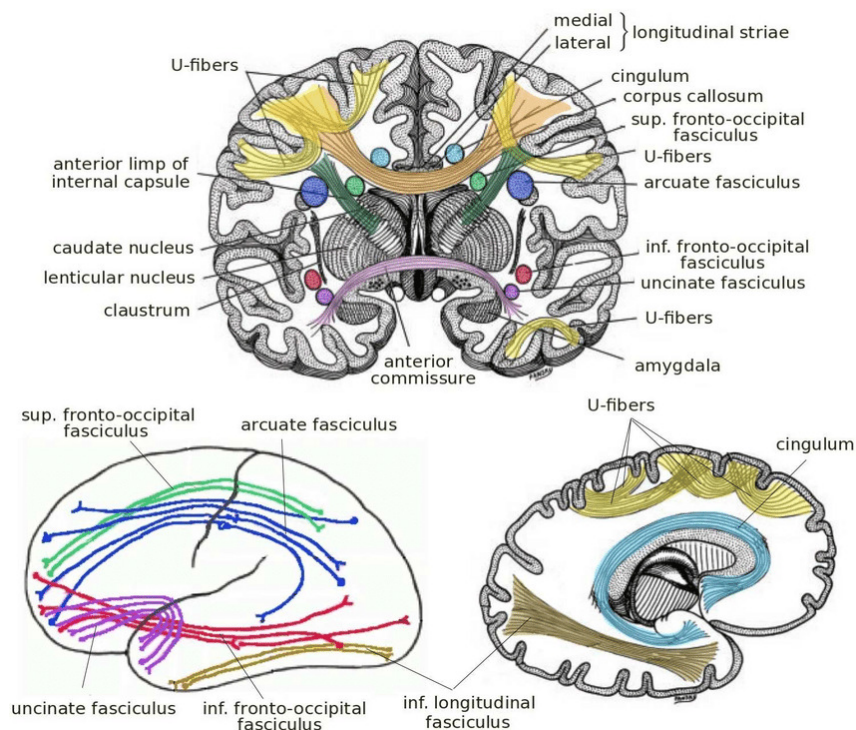
*Jellison et al. (2004) and Poupon (1999a)]

SCD group displayed significant decrease in FA in frontal superior fibers. aMCI and dementia group displayed significant FA decrease similar fibers compared to HC. No significant changes was measured in SCD compared to aMCI and dementia.

# MRI DTI: *White matter fibers mean diffusivity (MD)*

| DTI-MD p Value	HC vs. SCD	HC vs. MCI	HC vs. Dementia	SCD vs. MCI	SCD vs. Dementia	MCI vs. Dementia
Genu of corpus callosum'	0.01	0.08	0.00	0.70	0.19	0.14
Body of corpus callosum'	0.10	0.13	0.00	0.87	0.05	0.13
Splenium of corpus callosum'	0.42	0.04	0.00	0.16	0.00	0.15
Anterior corona radiata L'	0.12	0.22	0.11	0.93	0.79	0.76
Anterior corona radiata R'	0.11	0.21	0.05	0.93	0.52	0.53
Superior corona radiata L'	0.26	0.32	0.13	0.95	0.55	0.65
Superior corona radiata R'	0.31	0.30	0.13	0.85	0.51	0.69
Cingulum (hippocampus) L'	0.02	0.33	0.17	0.30	0.50	0.74
Cingulum (hippocampus) R'	0.03	0.29	0.21	0.45	0.53	0.89
Fornix L'	0.02	0.03	0.01	0.79	0.57	0.81
Fornix R'	0.04	0.02	0.03	0.56	0.63	0.91
Superior longitudinal fasciculus L'	0.20	0.35	0.26	0.87	1.00	0.89
Superior longitudinal fasciculus R'	0.20	0.26	0.21	0.96	0.89	0.94
Superior fronto-occipital L'	0.01	0.12	0.01	0.56	0.56	0.30
Superior fronto-occipital R'	0.04	0.13	0.01	0.84	0.29	0.28
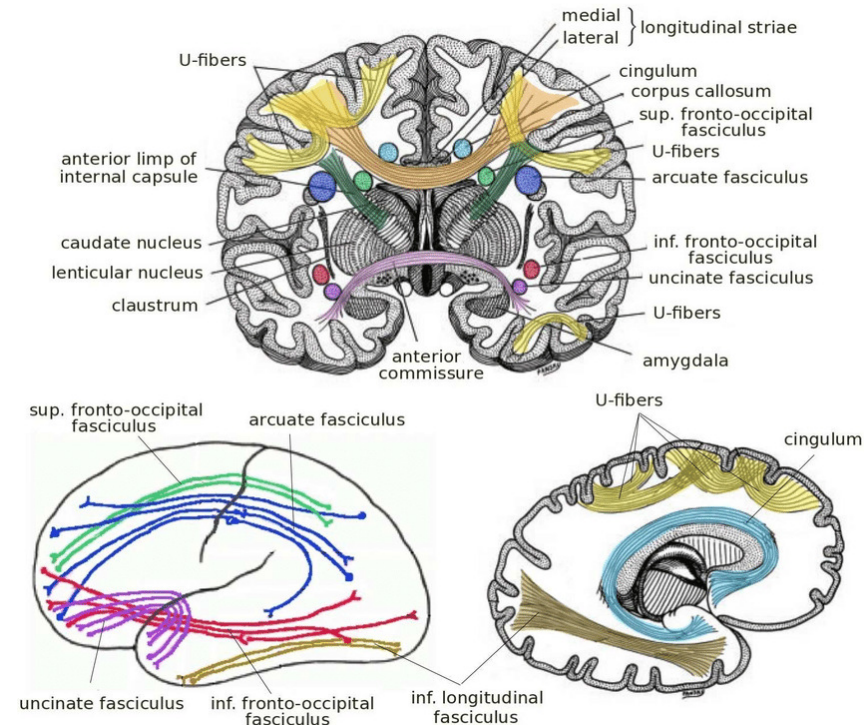
*Jellison et al. (2004) and Poupon (1999a)]

SCD group displayed significant increase in MD frontal tracks and Cingulum, aMCI group displayed significant MD increase in fornix and rear CC only compared to HC and SCD. Dementia subjects displayed significant MD increase in CC ,Fornix and superior fronto-occipital fibers.

Functional - *DELPHI direct electrophysiological imaging*
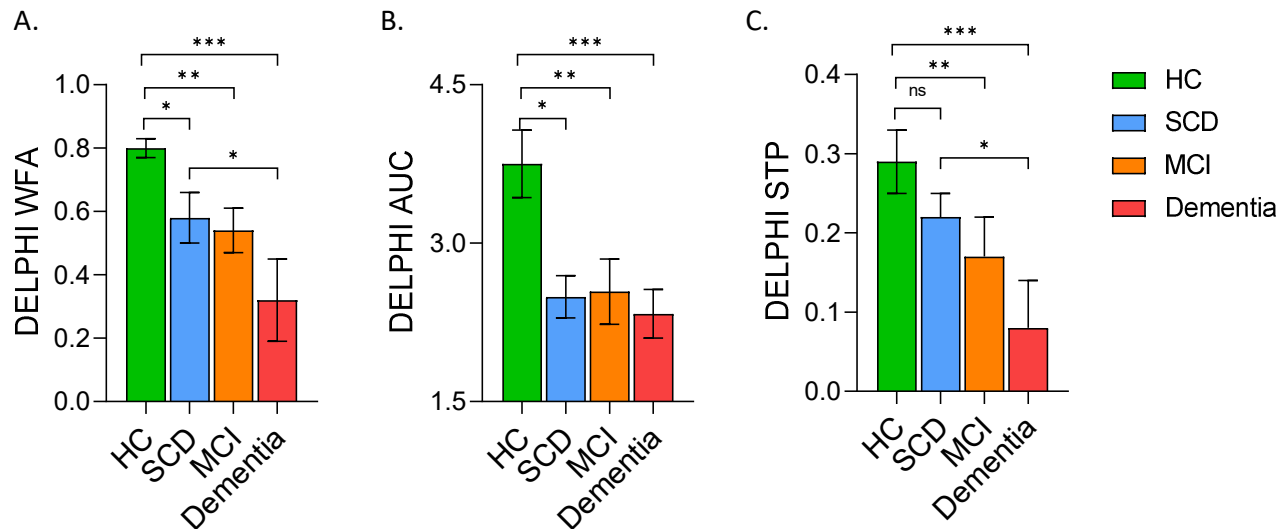
Main conclusion: SCD group displayed significant decrease in WFA and AUC indicating changes in network connectivity and excitability compared to HC. aMCI and dementia group displayed significant decrease in WFA, AUC and STP compared to HC. Dementia group displayed decreased WFA and STP in compared to SCD
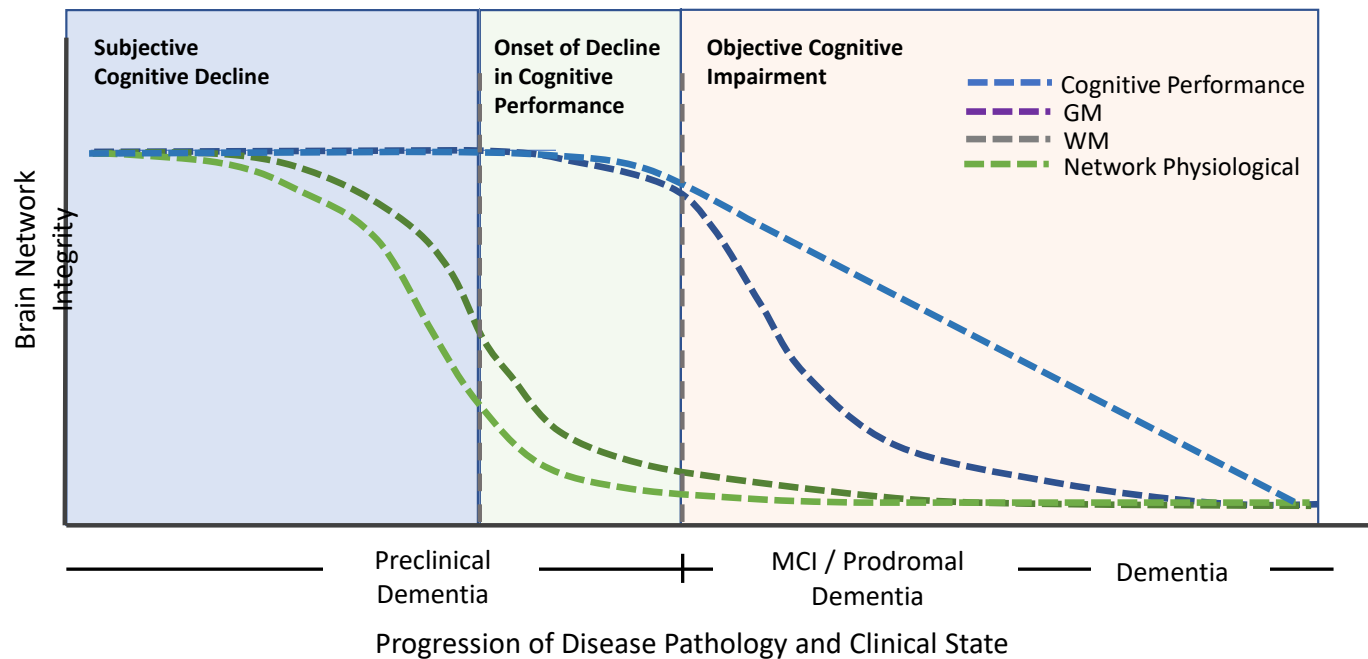
Objective direct measures of brain network physiology and WM integrity may provide early-stage neuro-biomarkers in subjects that have not yet displayed any other objective measurable cognitive or GM volume deficits which may facilitate early preventive care.

DELPHI AS A DIAGNOSTIC AID

Decision tree recommendation

- Delphi
  - **Normal** → Clinical\Cognitive findings independent of Delphi
    - **No** → Probably Healthy → Return for periodic review
    - **Yes** → Clinical\Cognitive findings are most probably not related to major atrophy or cerebrobrovascular disease → Proceed for further investigation (psychiatric\mood\ other)
  - **Abnormal** → Clinical\Cognitive findings independent of Delphi
    - **No** → High probability of silent (asymptomatic) cerebrovascular disease –Risk for stroke and dementia → Further investigation and Preventive care recommended by AHA/ASA guidelines for primary prevention of ischemic stroke and other cerebrovascular diseases
    - **Yes** → High probability of cerebrovascular related diseases: VaD, VCI, mixed dementia, AD, cSVD, Stroke → Proceed to diagnosis and treatment according to clinical findings of severity and nature of cognitive \clinical findings and domains