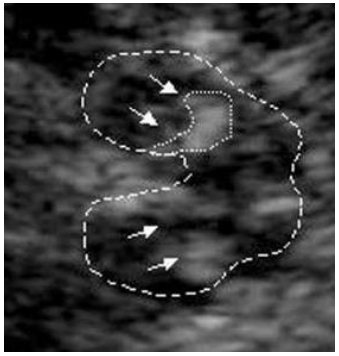
La neurosonologia

Nelle patologie degenerative e vascolari cerebrali

Andrea Pilotto



Ecografia cerebrale e nuove applicazioni nelle malattie neurodegenerative

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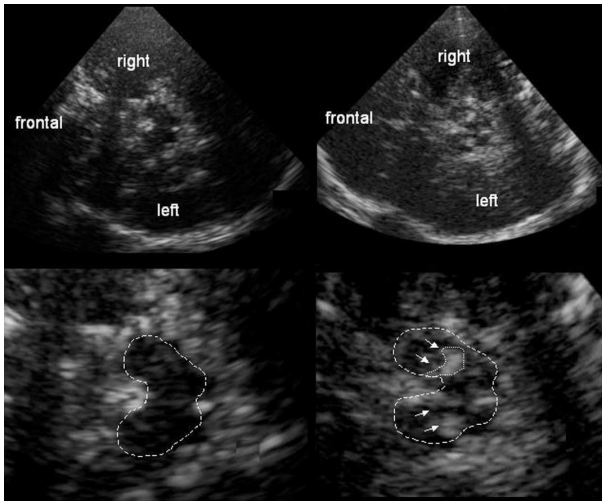
Neurology Unit
Department of Clinical and Experimental Sciences
University of Brescia, Italy

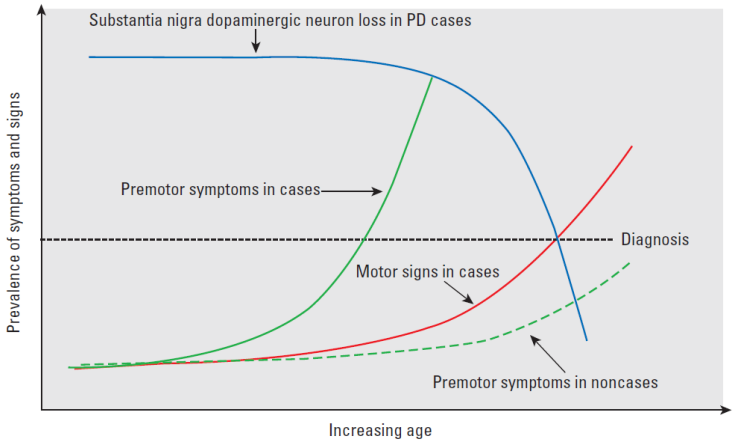
Anatomy and method: the TCS



TCS in differential diagnosis of parkinsonism

TCS in dementia

TCS in proprodromal disease stages



New research directions

Anatomy and method: the transcranial ultrasound (TCS)

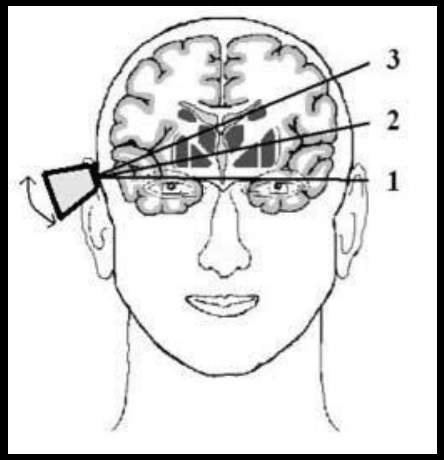
Advantages:

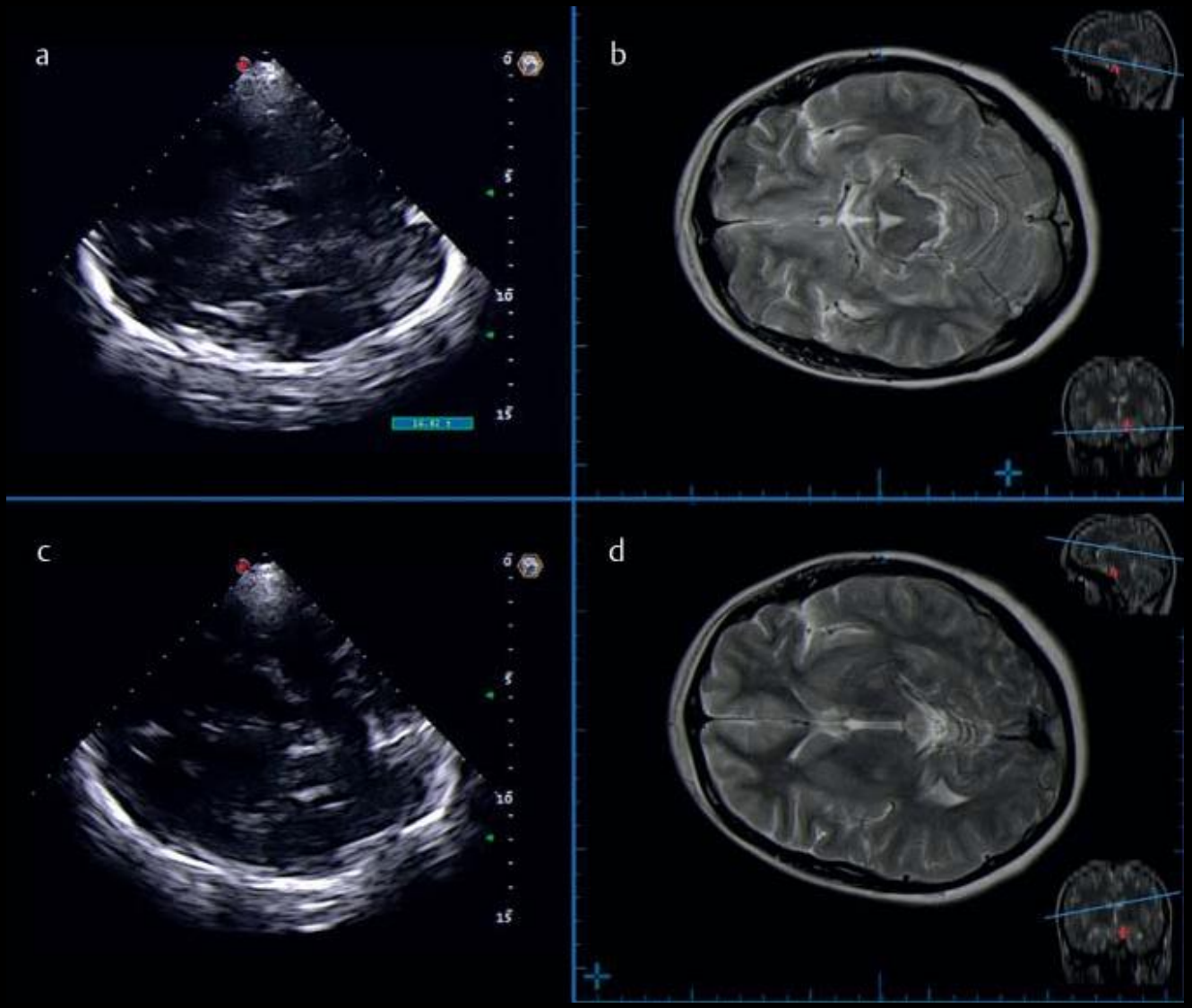
- Non-invasive
- Cheap
- Fast
- Mobile
- No effect with patient‘s head movements
- Unlimited repeatability

Disadvantages:

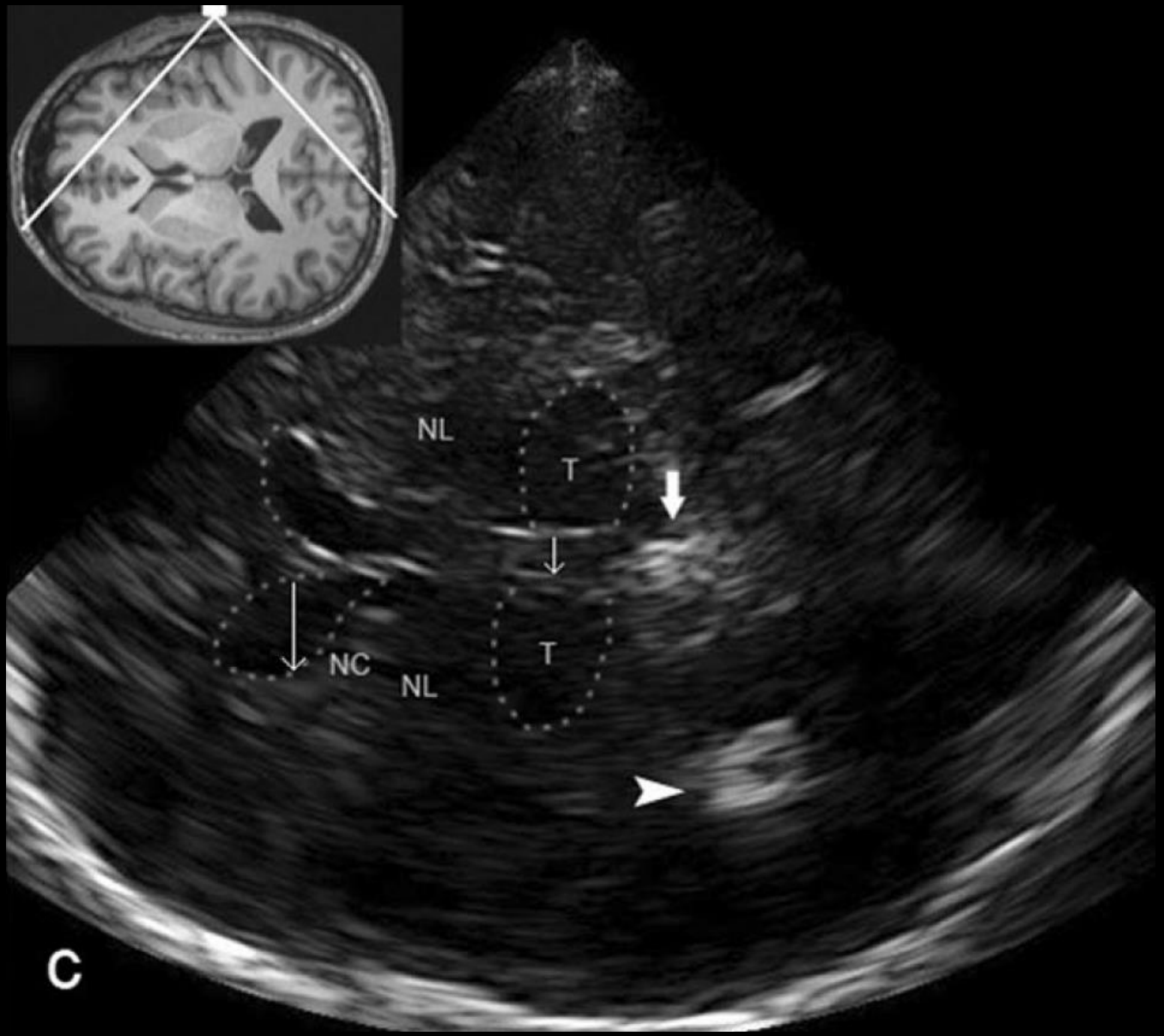
- Needs expertise
- Depends on temporal bone window (10-15% no window)
- Different cut-off values with different machines and populations

Different planes





Walter et al. Ultraschall Med 2014


NL
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NC
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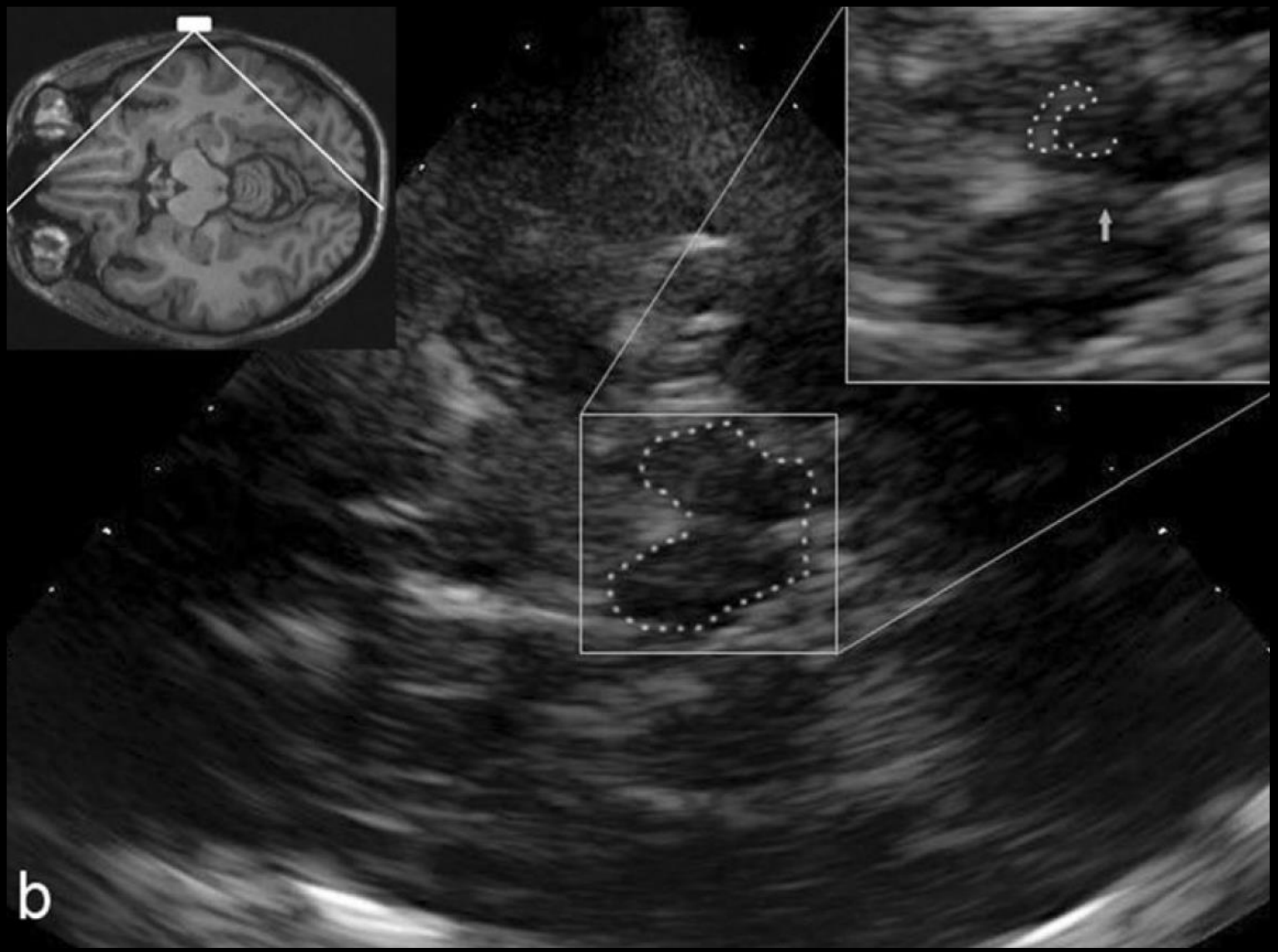
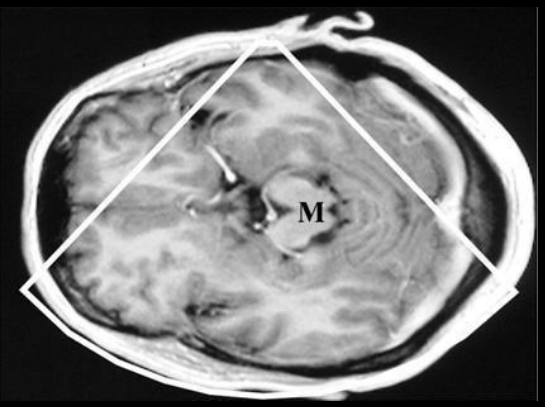
C

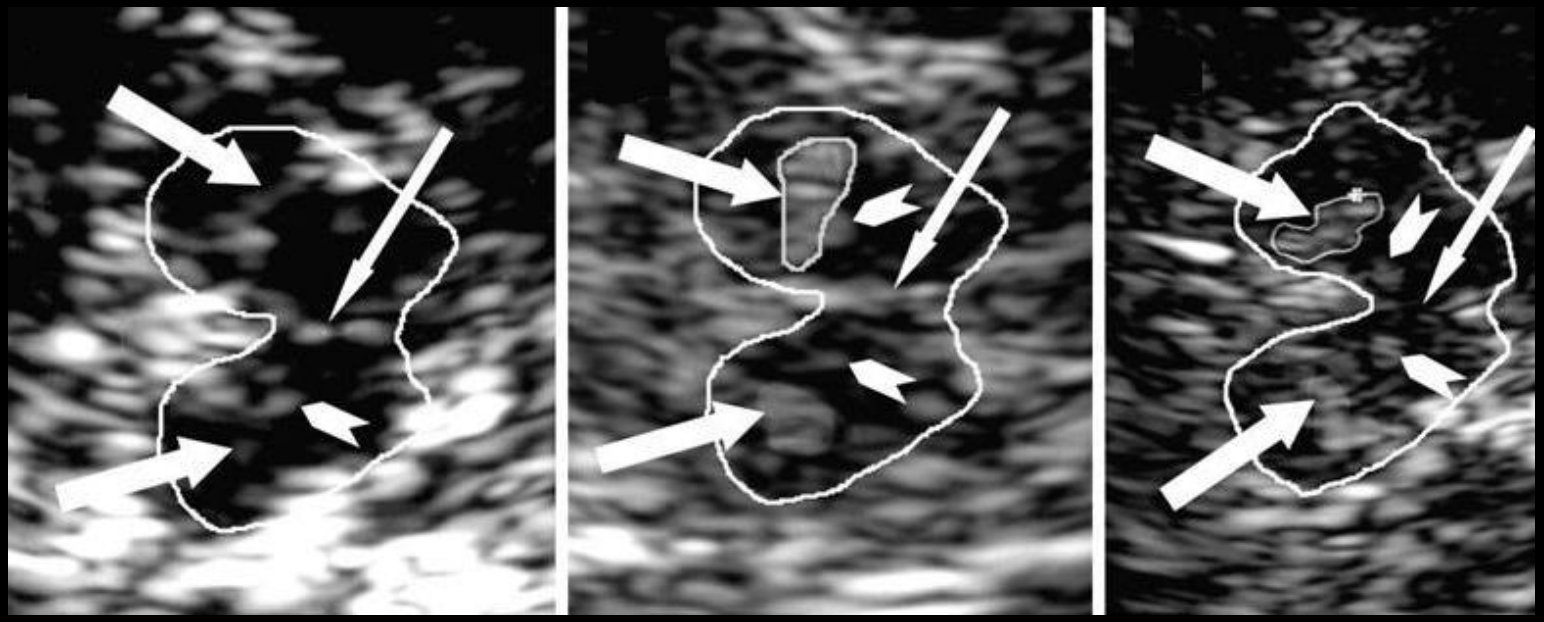
Midbrain plane





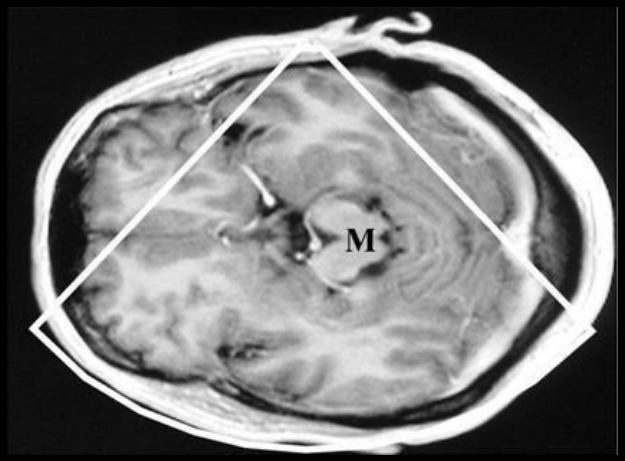
Reduced echogenicity of the midbrain raphe

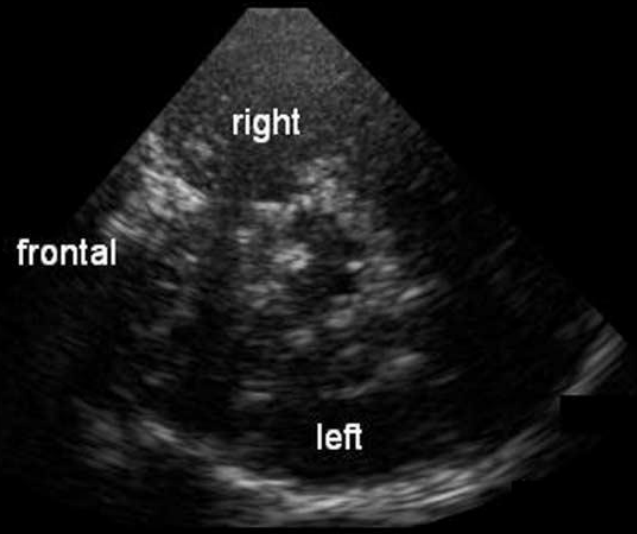
- 10 % of the normal population
- 50 – 70 % of patients with depressive disorders.

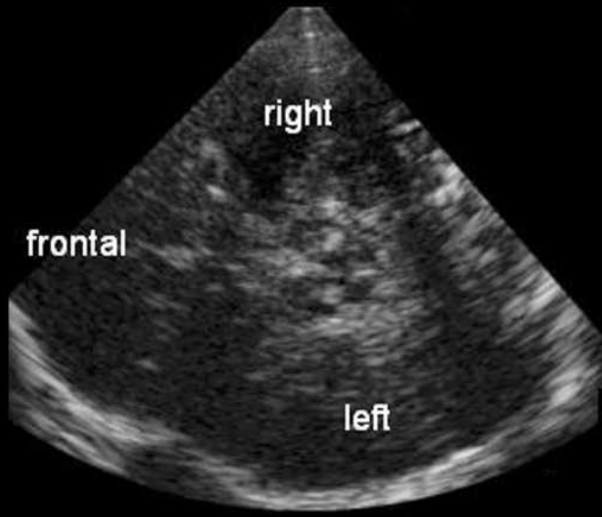


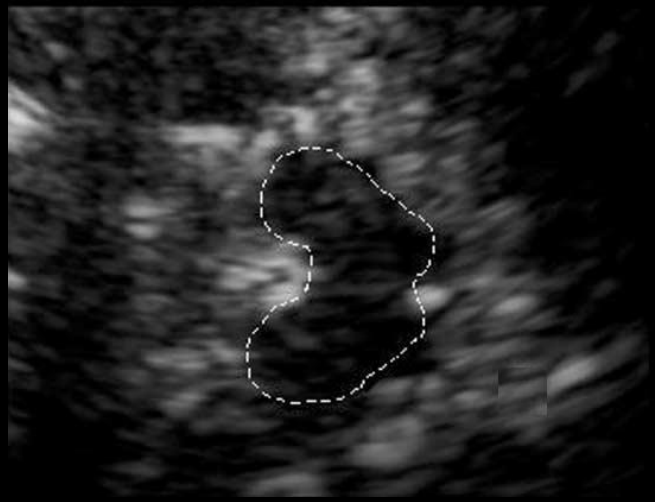
Walter et al. Brain 2007

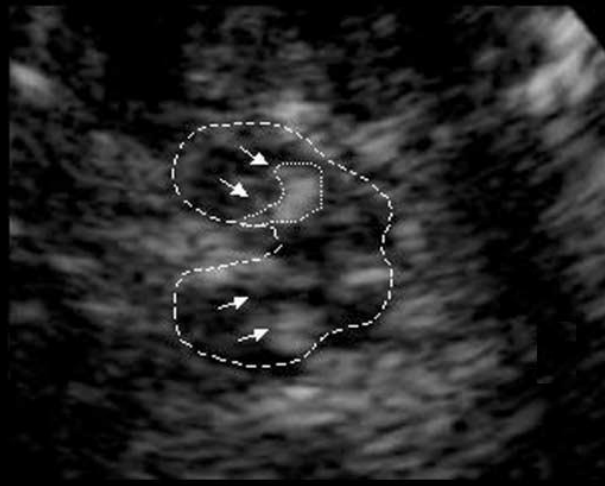
SN hyperechogenicity



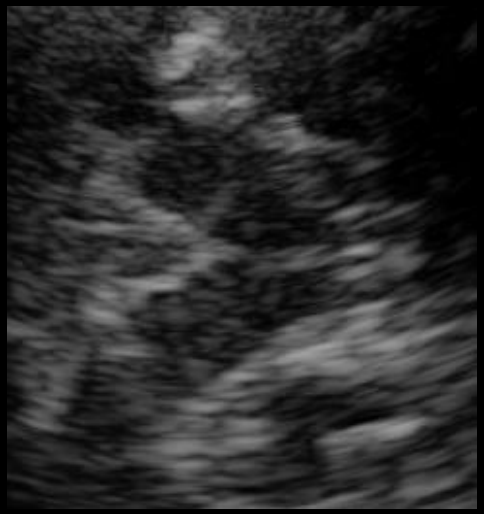






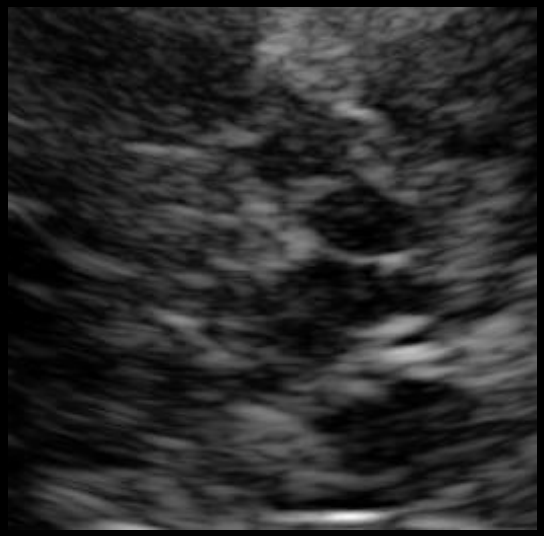


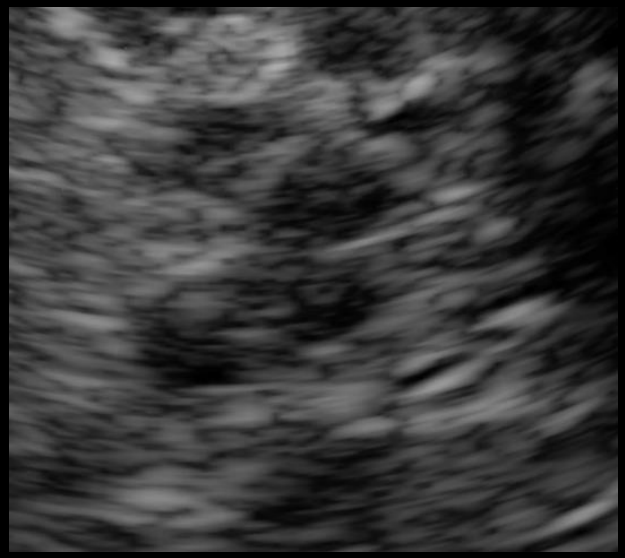
SN hyperechogenicity evaluation

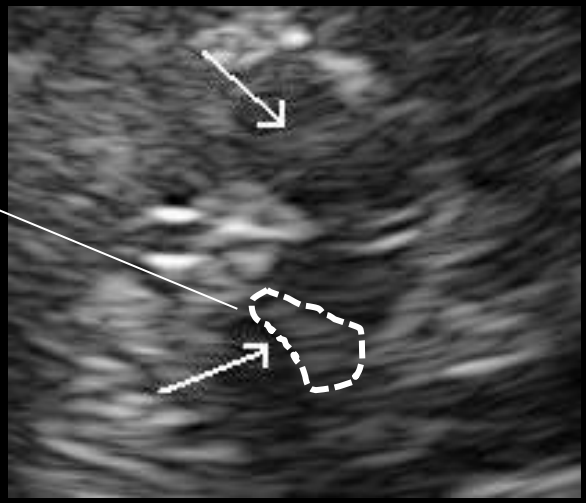


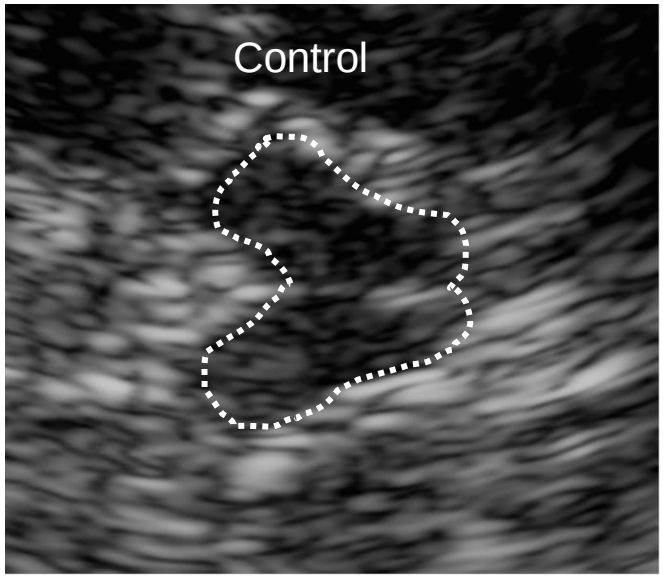
Grading:
Isoechogenic
Mildly echogenic
Hyperechogenic

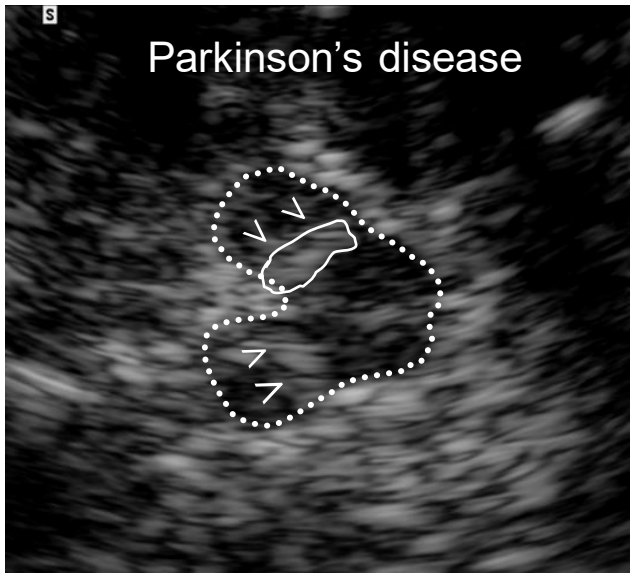
SN planimetric measurement

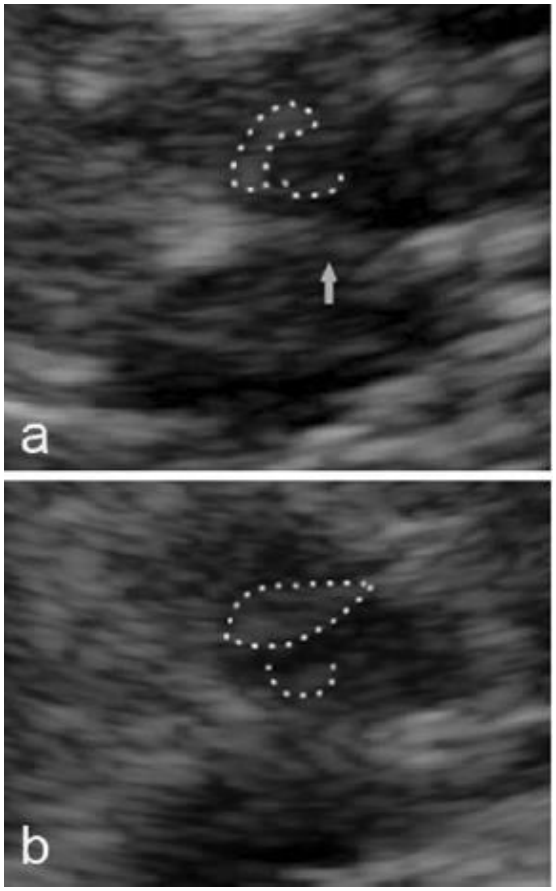












Prevalence in Parkinson's disease > 90%

(Berg et al., 2001; Walter et al., 2002)

Independent publications

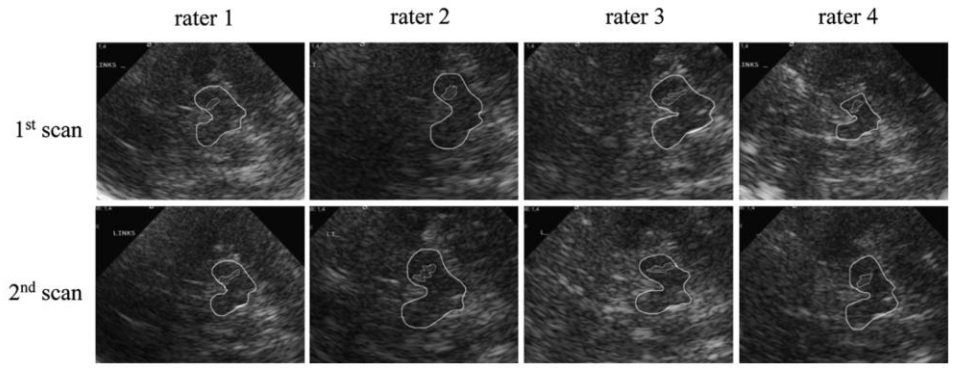
Sommer et al., 2004; Spiegel et al., 2006; Tromp et al., 2005; Ressner et al., 2005; Skoloudik et al., 2005; Zedde et al., 2005; Hagenah et al., 2006; Iova et al., 2005; Miranda et al., 2006 ; Wu et al., 2007; Behnke et al. 2009, Hellwig et al. 2014 Shu et al. 2014, Li et al., 2015,...

SN Cut-off standardisation

Cut-offs should be calcolated for:

1) Different machines
2) Different populations

manufacturer/ ultrasound system	probe/ frequency [MHz]	cut-off value [cm²]		references
		SN-h[1]	Marked SN-h[1]	
Aloka/Prosound Alpha 10	UST-52 105/2.5	≥ 0.19	≥ 0.25	Mijajlović et al. [20]
Esaote/MyLab25 Gold	PA240/2.5	≥ 0.20	≥ 0.25	Go et al. [3]
Esaote/MyLab Twice	PA240/2.5	≥ 0.24	≥ 0.30	(own data)
General Electric/Logiq 7	3S/2.5		≥ 0.24	Stockner et al. [21]
General Electric/Logiq 9	3S/2.5	≥ 0.20		Fedotova et al. [22]
Philips/HDI 5000 SonoCT	P2 – 4/2.5	≥ 0.20		Kim et al. [23]
Philips/HP Sonos 5500	S4/2.0 – 2.5	≥ 0.20	≥ 0.27	Mehnert et al. [17] Hagenah et al. [18]
Siemens/Acuson Antares	PX4 – 1/2.5	≥ 0.24	≥ 0.30	Van de Loo et al. [10] Glaser et al. [24]
Siemens/Sonoline Elegra	2.5PL20/2.6	≥ 0.20	≥ 0.25	Berg et al. [16]
Toshiba Aplio XG	PST-20CT/2.5	≥ 0.16	≥ 0.22	Vivo-Orti et al. [25]



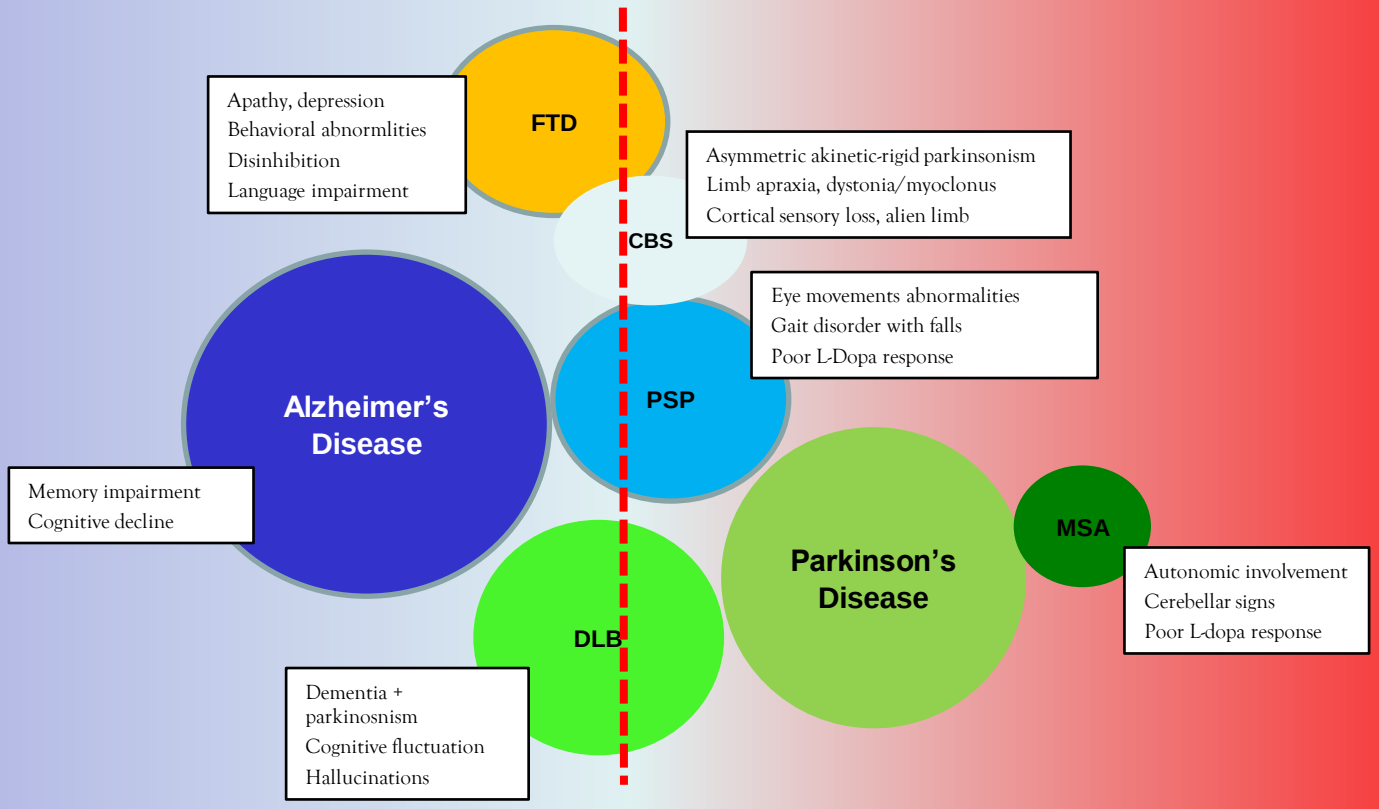
100 Healthy adult subjects

90th percentile should represent the cut-off in the healthy population

TCS in differential diagnosis of Parkinsonism

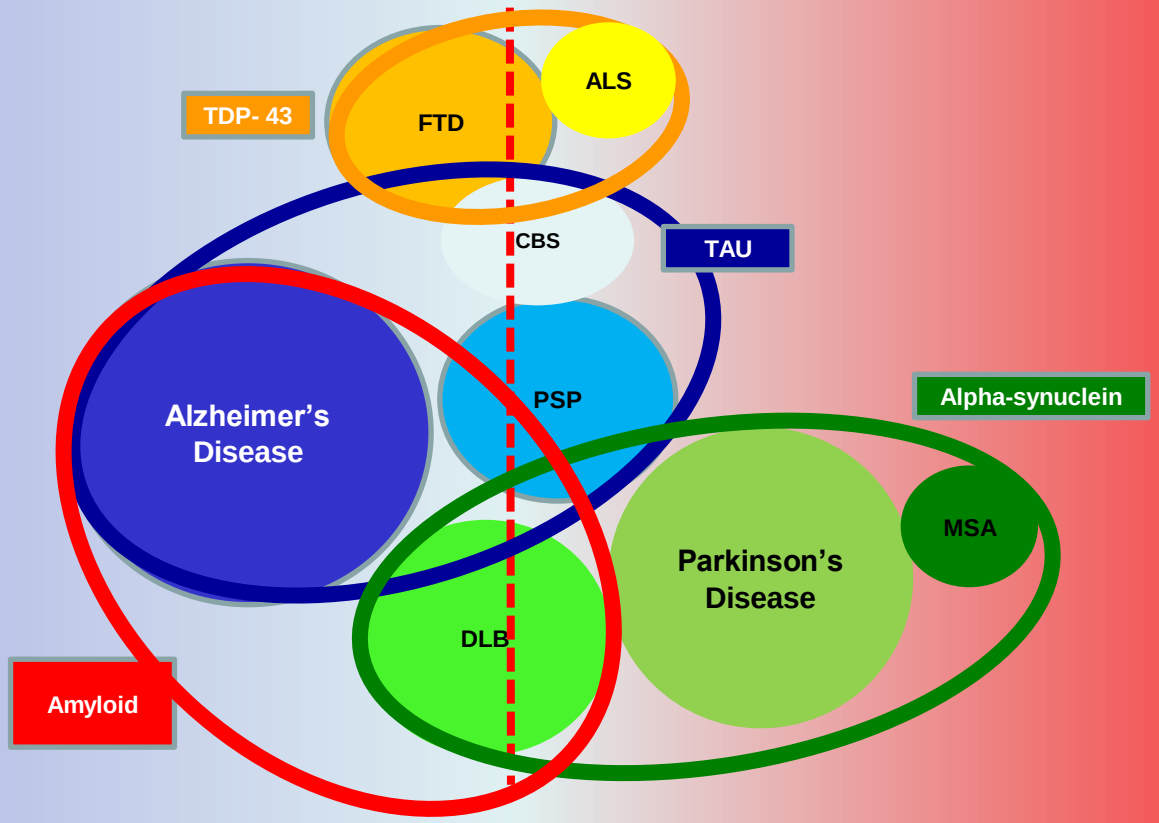
Dementia

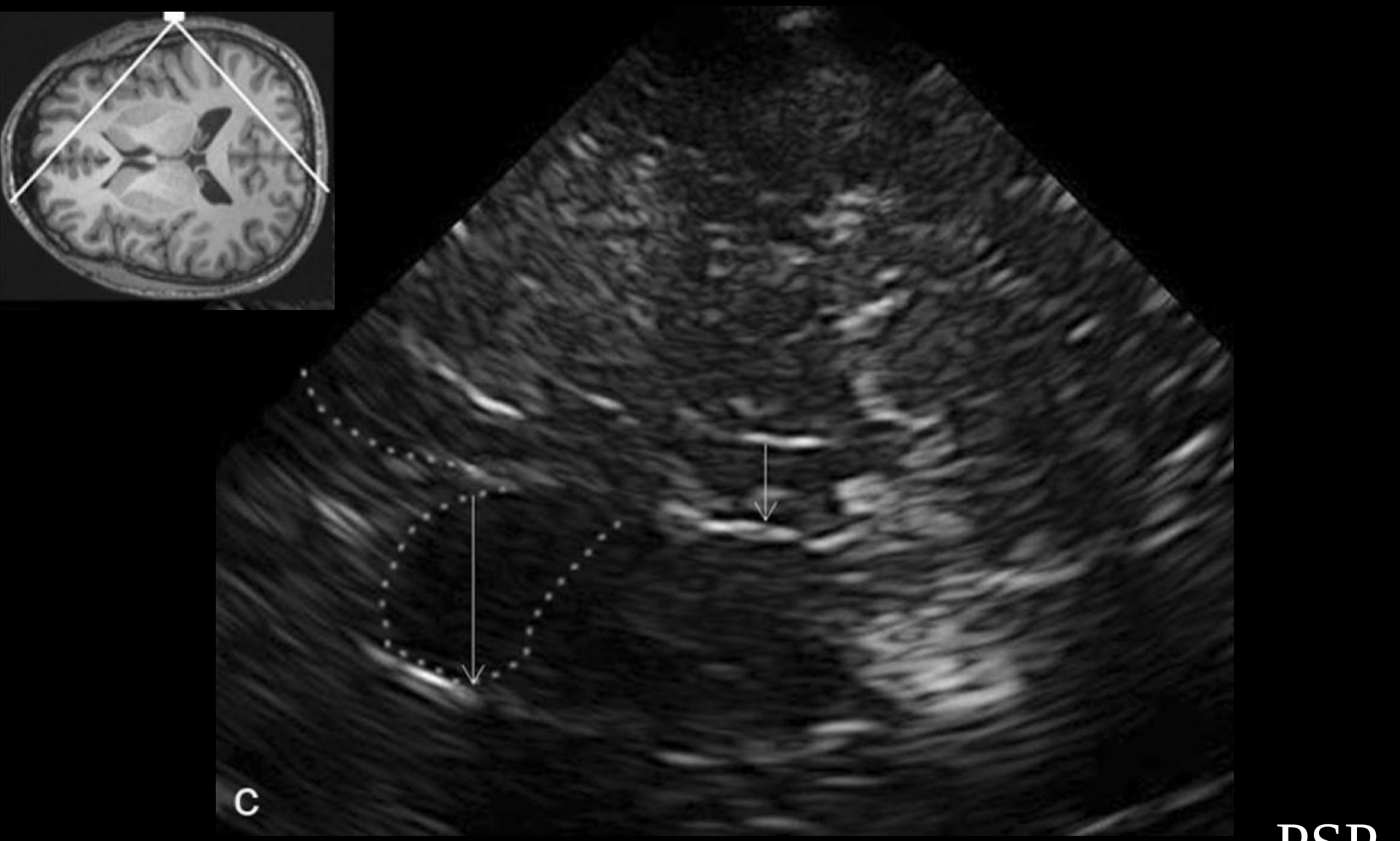
Parkinsonism



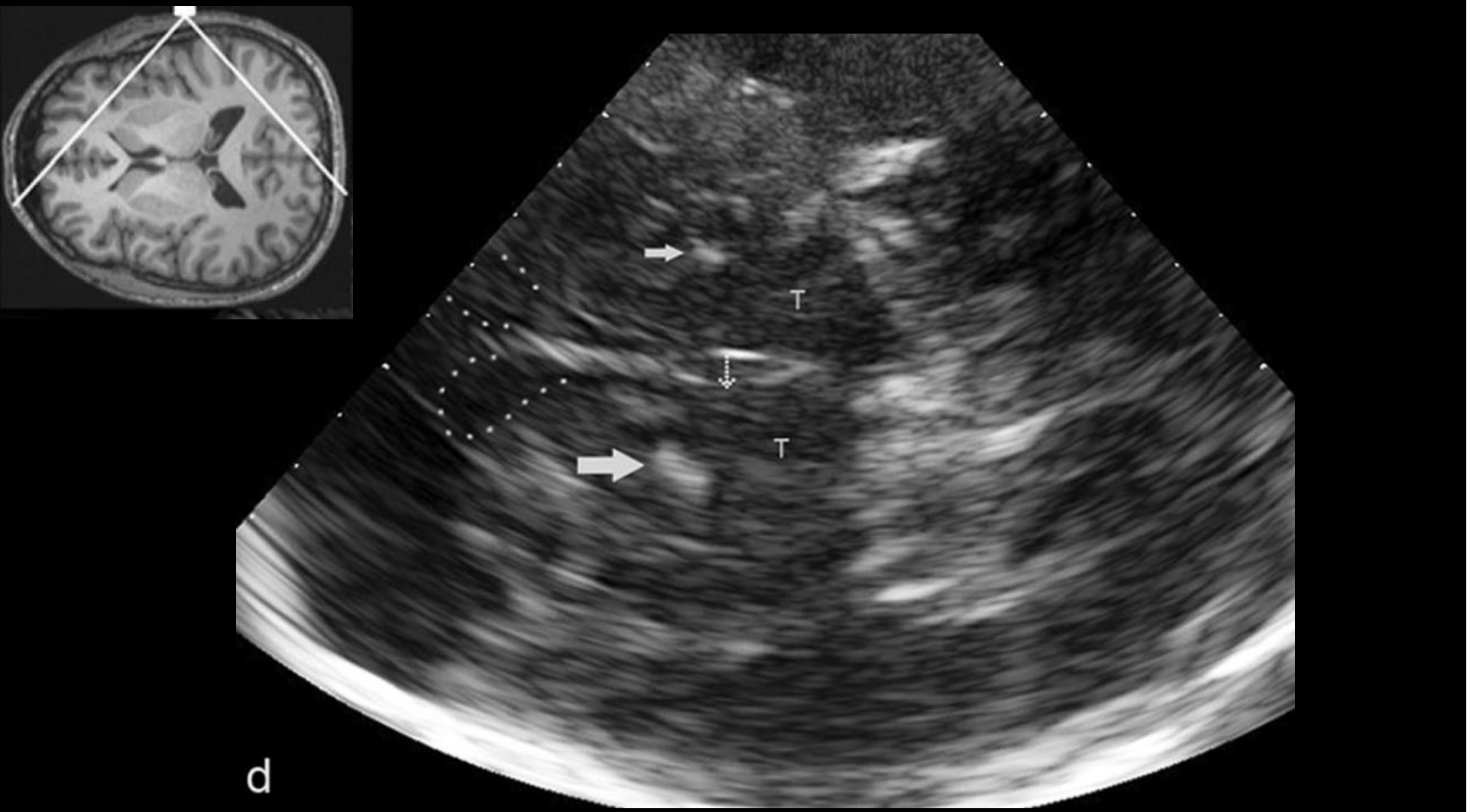
Dementia

Parkinsonism



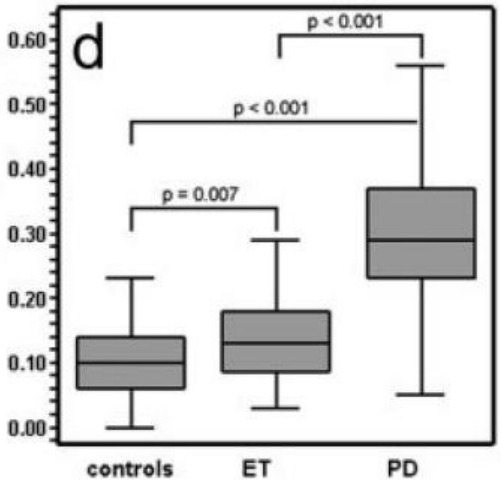


PSP



MSA

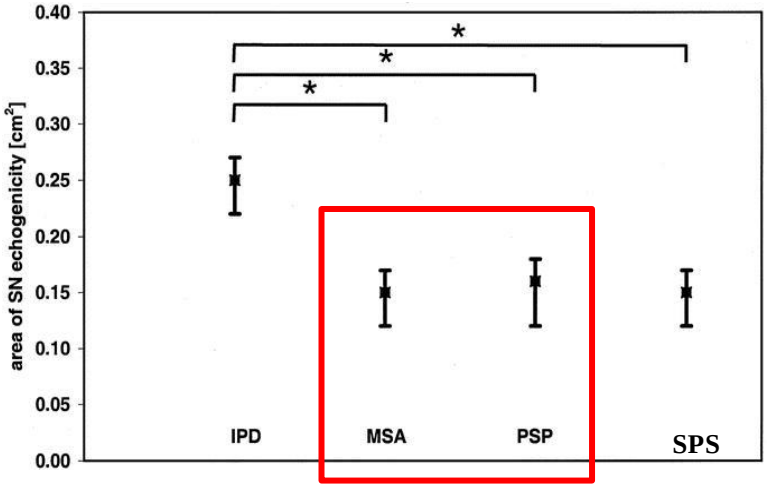
SN in differential diagnosis of tremor?



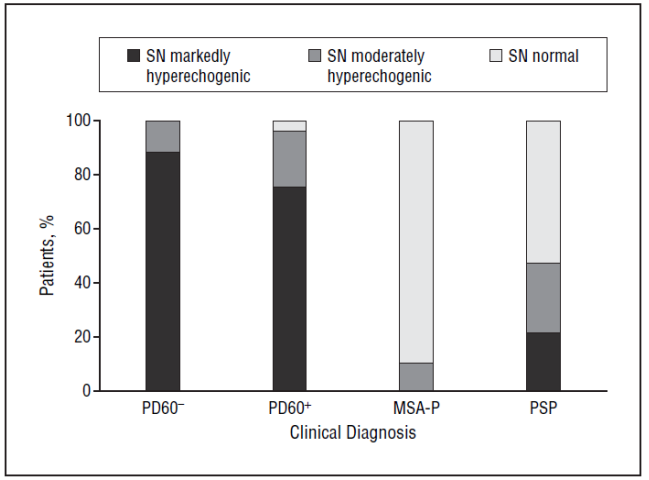
Comparison
44 ET, 100 PD, 100 HC
(Stockner et al. Mov Disord 2007)

SN+:
8-10% of normal population
33% of ET – SN+

SN in differential diagnosis of parkinsonism?



Walter et al. Neurology 2003



Walter et al. Arch Neurol 2007

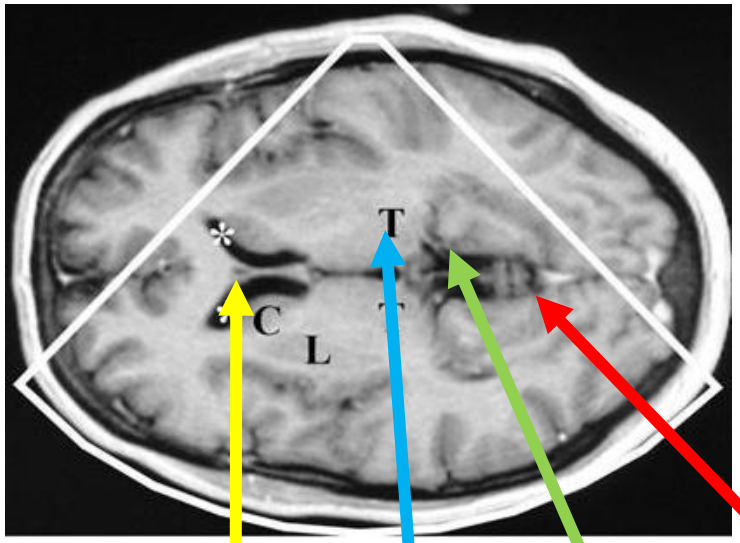
Disease	Substantia Nigra	Raphe	Ventricles	Basal ganglia
Sporadic PD	↑↑	↓	-	-
Atypical PS	-	-	↑↑ 3. Ventricle	↑↑
PSP	↑/-	-	-	↑↑
Metabolics		-	-	↑↑
Hydrocephalus	-	-	↑↑	-
Essential Tremor	(↑)	-	-	-

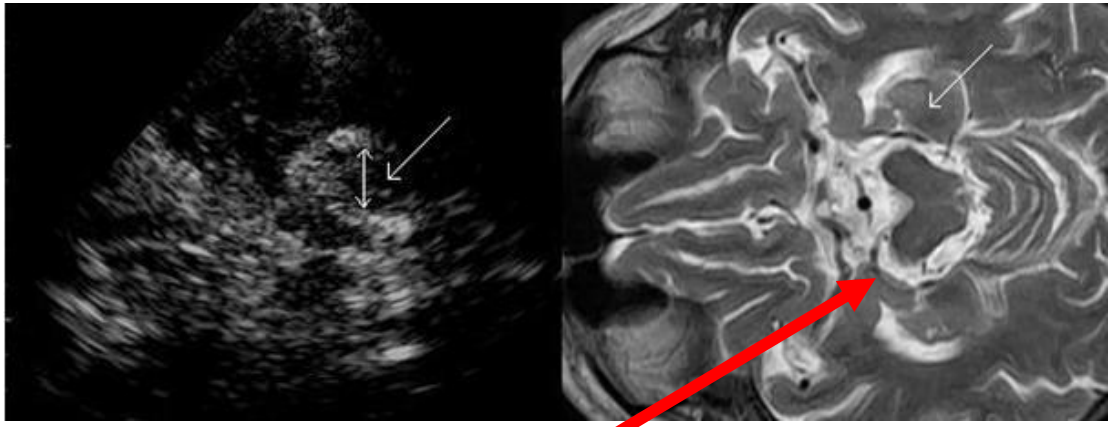
Table 1 Diagnostic accuracy of TCS in parkinsonism differential diagnosis

	Indicated condition	Exclusion condition	Sensitivity	Specificity	References
SN+	PD	Controls or ET	78–100	81–92	[7, 22•, 23, 50, 53•, 95–97]
SN+	PD	MSA + PSP	82–98	70–100	[30, 31, 36]
SN− and LN+	MSA or PSP	PD	56–59	99–100	[30, 31]
3 V (>10 mm) and LN+	PSP	PD	84	98	[30]
Combined SN, LN hyperechogenicity and 3 V	PD, PSP, CBS, MSA differential diagnosis		82	85	[29••, 36]

Pilotto et al. 2015

From parkinsonism to dementia..



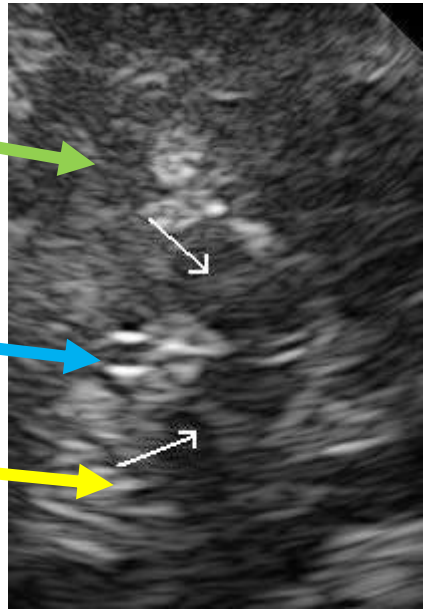


Alzheimer's disease

Parkinson's Dementia

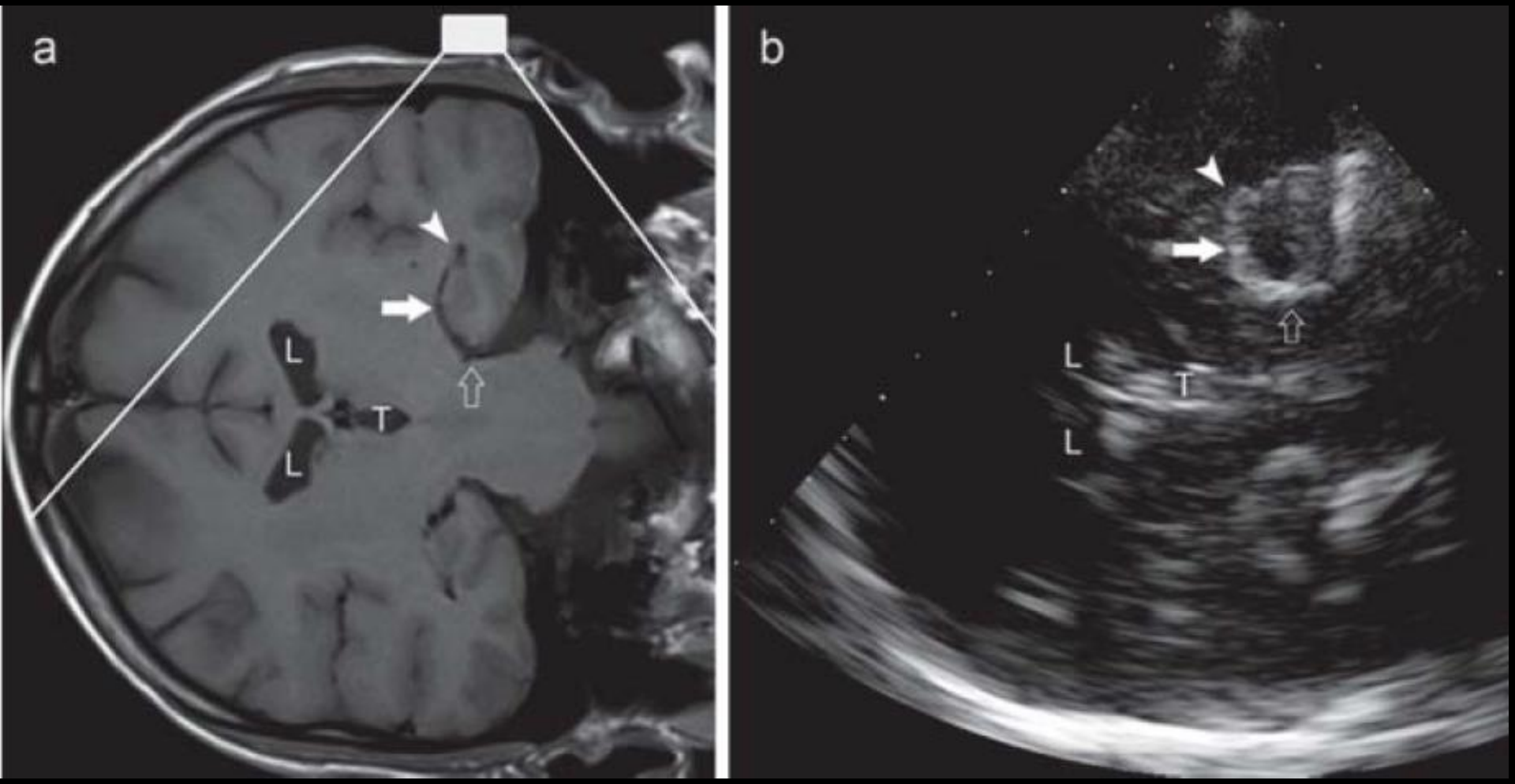
Dementia with Lewy bodies

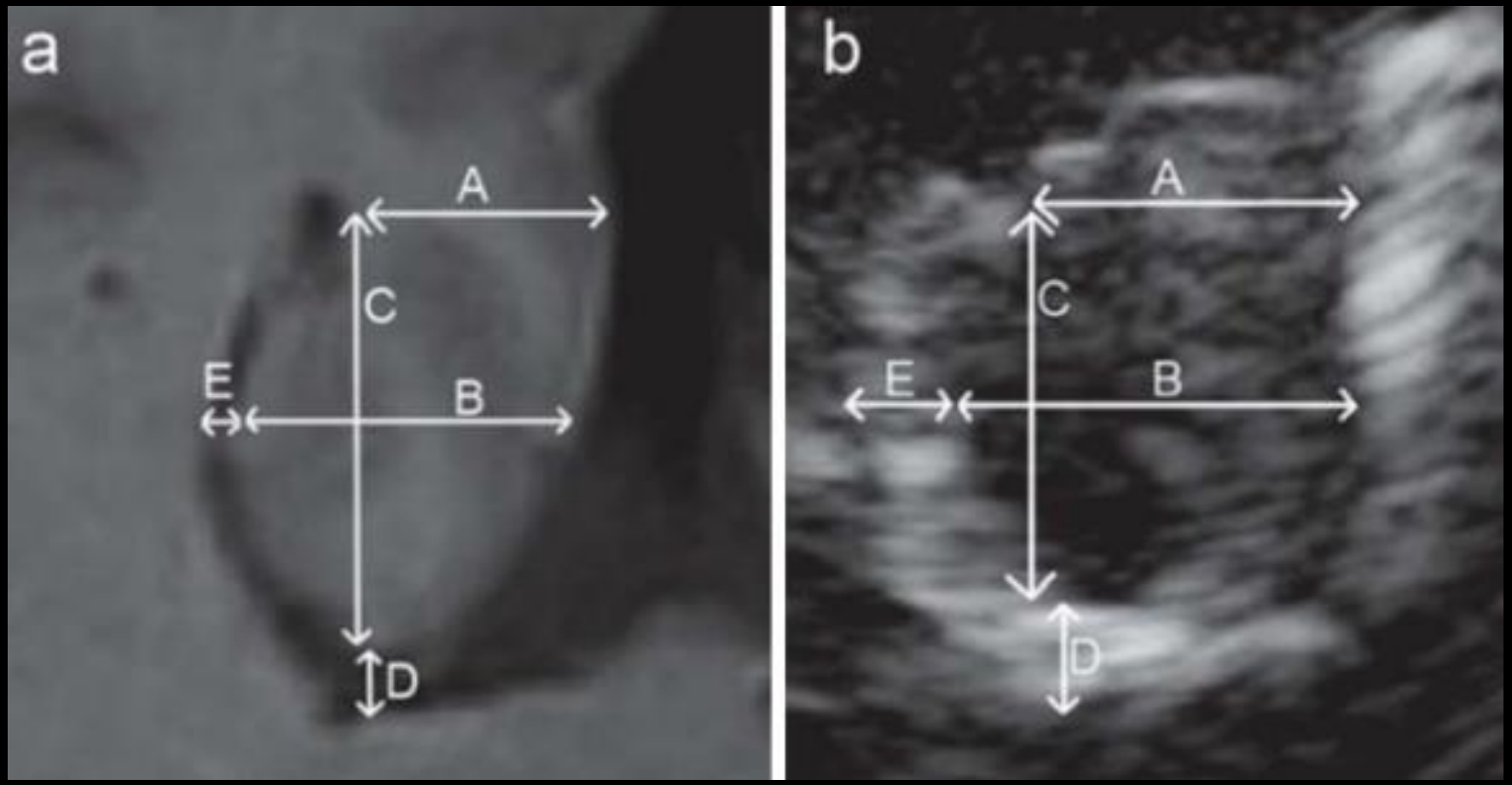
Frontotemporal dementia



Structural Ultrasound of the Medial Temporal Lobe in Alzheimer's Disease

R. Yilmaz[1], A. Pilotto[1, 2], B. Roeben[1, 3], O. Preische[3, 4], U. Suenkel[1], S. Heinzel[1], F. G. Metzger[4, 5], C. Laske[3, 4, 5, 6], W. Maetzler[1, 3], D. Berg[1, 3, 7]

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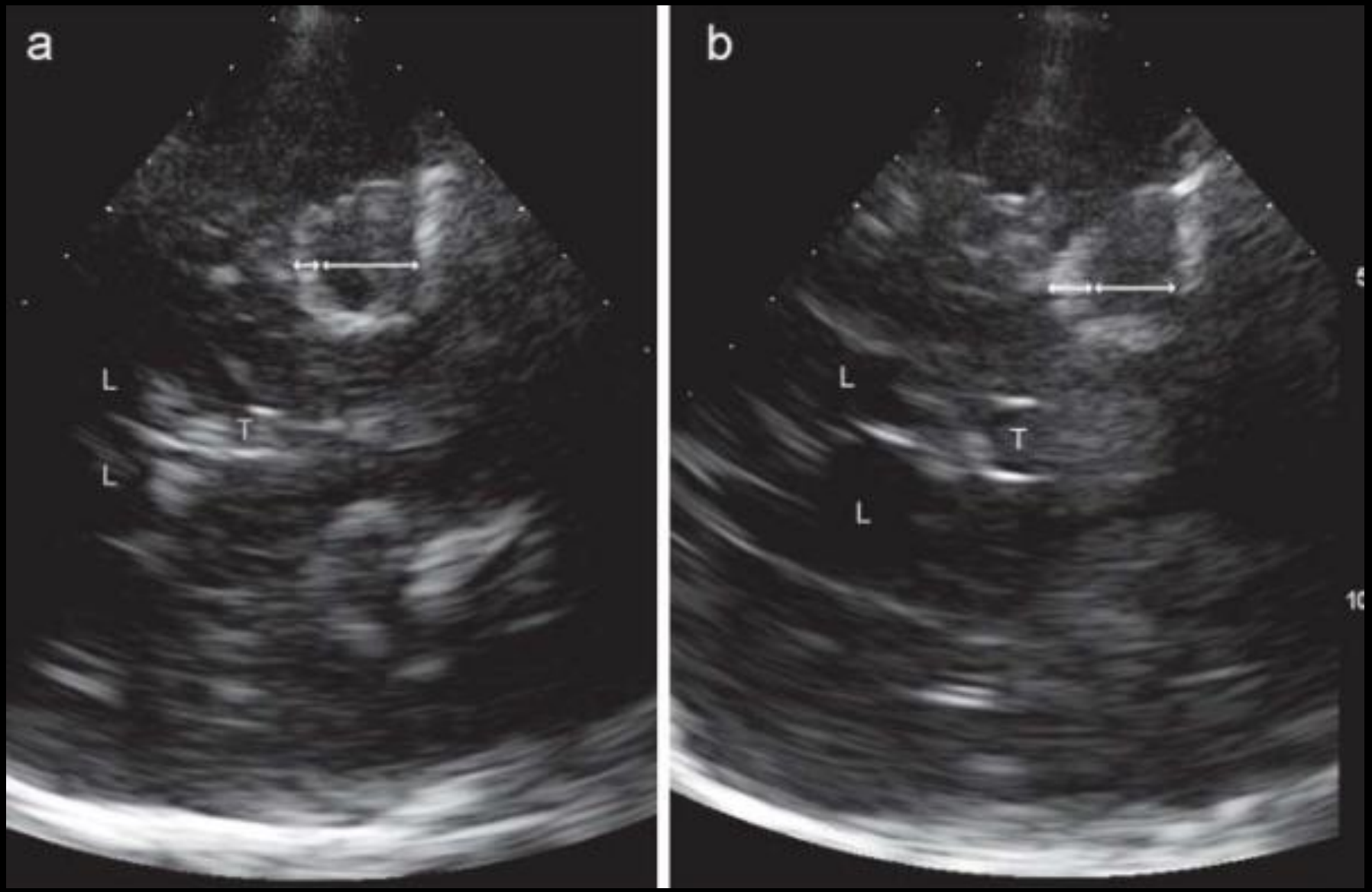
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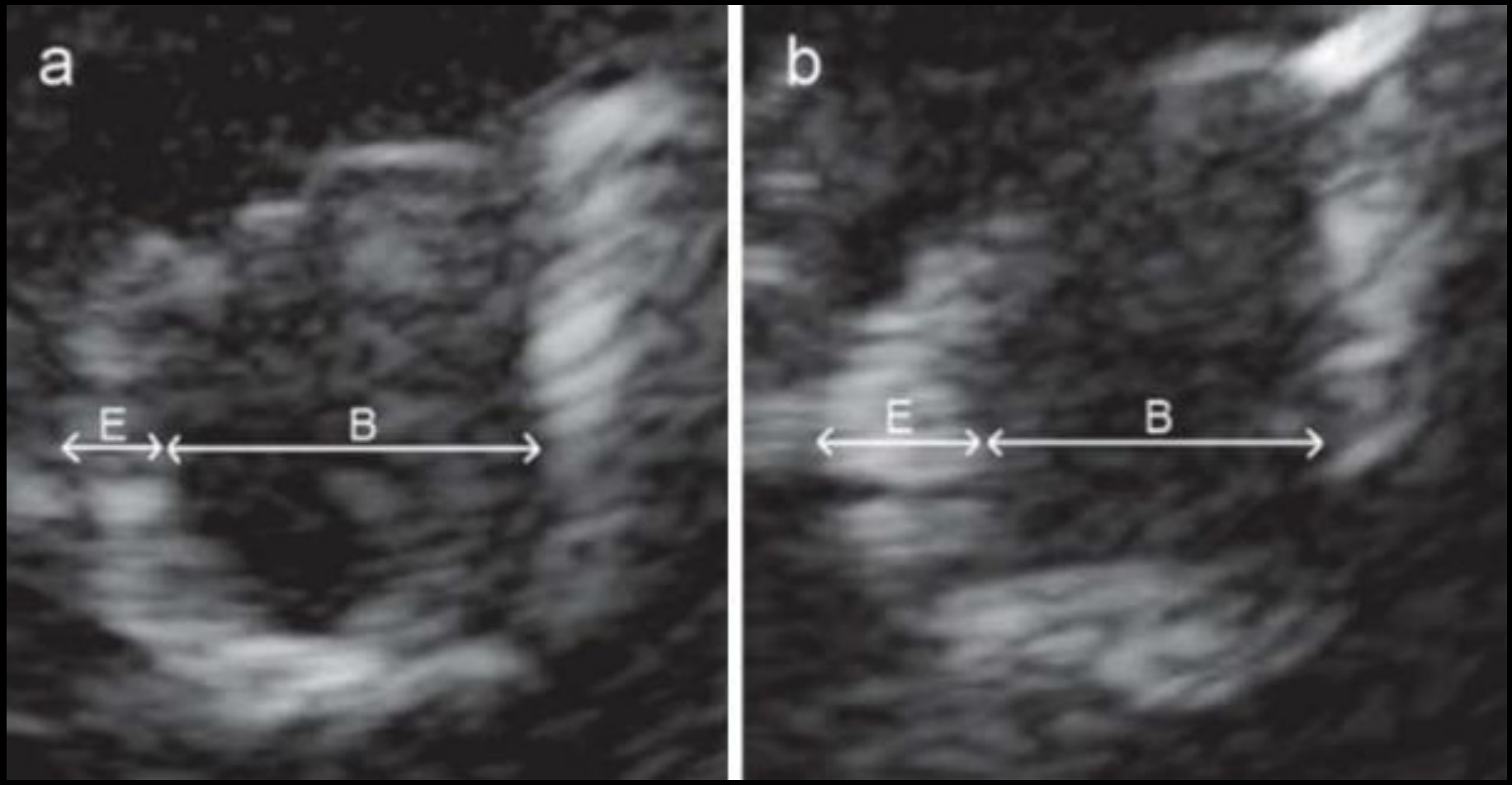


The B/E ratio≤ 2.5 separated two groups with a sensitivity of 83 % and a specificity of 76 %, with an area under the curve (AUC) of 0.81

SN and TCS in prodromal neurodegeneration

about 8-10 % of healthy adults display increased echogenicity similar to Parkinson's disease

Is there any functional relevance of increased SN-echogenicity in healthy subjects?

Association with signs of motor retardation in elderly people

Berg et al., 2001, Behnke et al., 2007

Found in asymptomatic mutation carriers for monogenetic PD and associated with positive family history

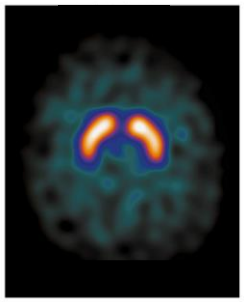
Walter, et al., 2003; Schweitzer et al., 2007

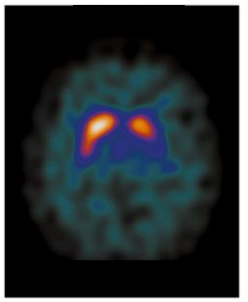
Relation of SN hyperechogenicity, olfactory dysfunction and SPECT abnormality

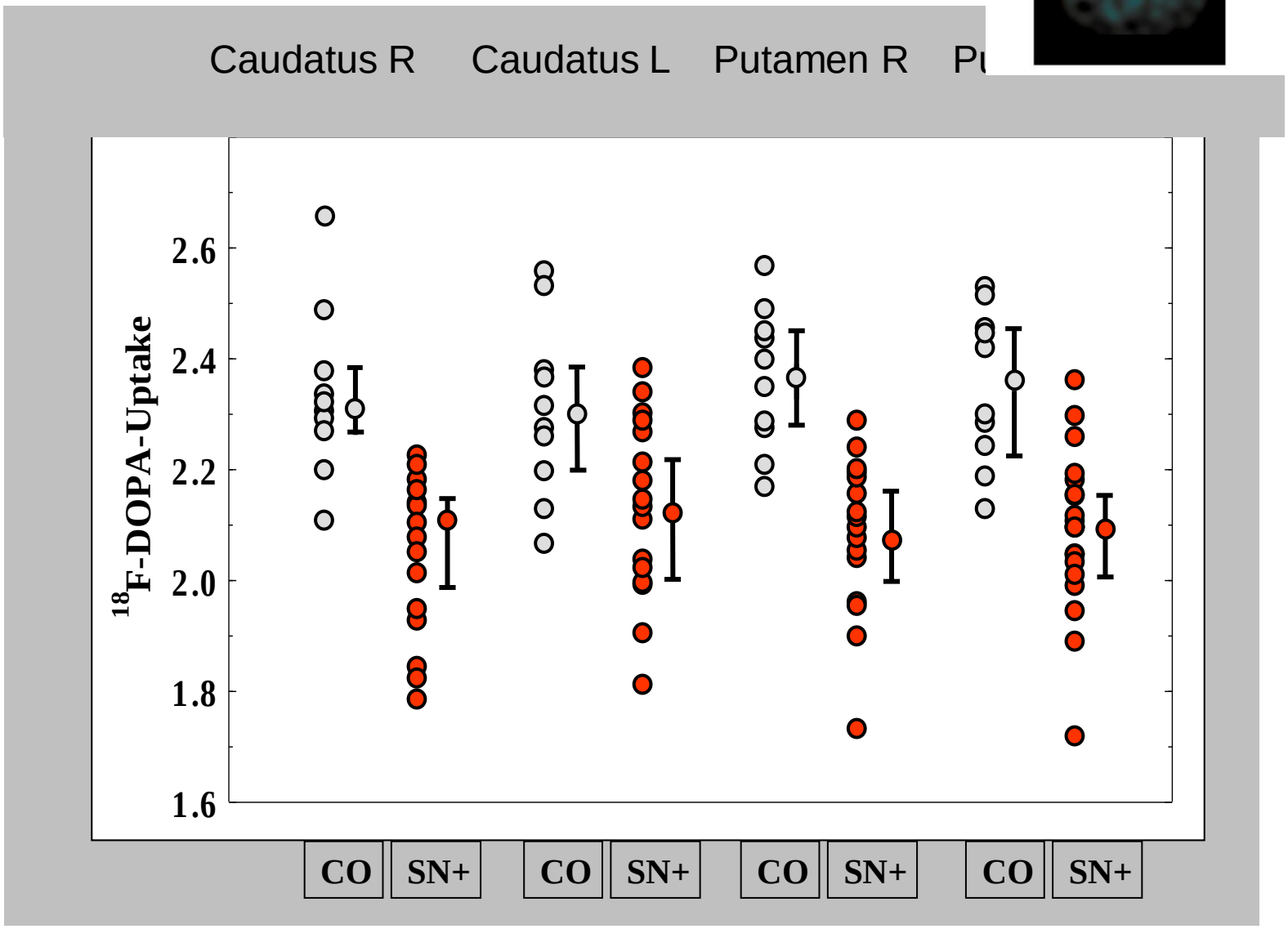
Sommer et al., 2004, Haehner et al., 2007

Relation of SN hyperechogenicity and REM sleep behaviour disorder

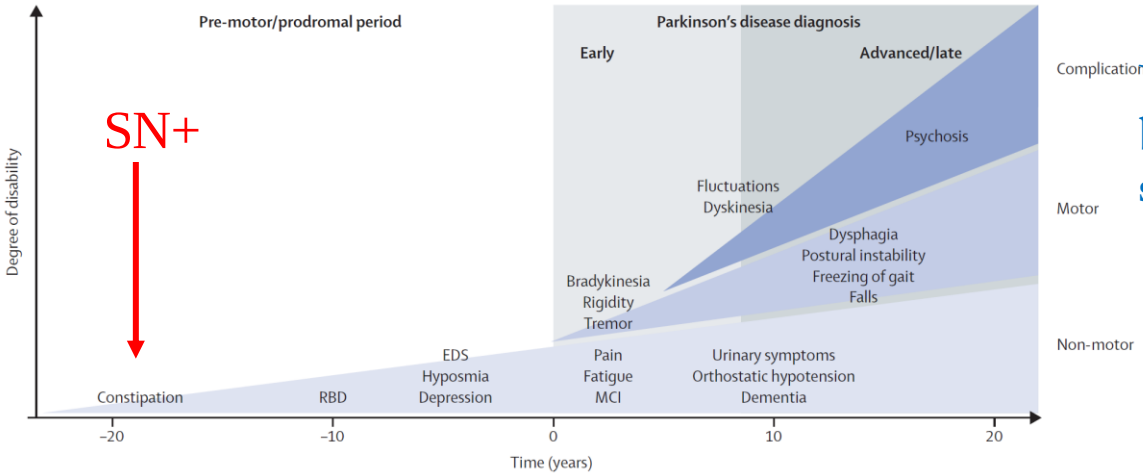
Unger et al., 2008







Berg et al. Neurology 1999; Arch Neurol 2002



Khalia et al. Lancet Neurol 2015

Up to 2006, development of PD had been observed in at least 14 healthy subjects with SN hyperechogenicity

Parkinson – Premotor Prospective Studies - PRIPS

Baseline assessment

1847 subjects

254 SN+

→

8/10 PD patients SN+

3 years:

RR = 17.37

PPV = 3.1%

→

14/17 PD patients SN+

5 years:

RR = 20.6

PPV = 6.5%

Berg et al. Arch Neurol 2011,
Berg et al. Mov Disord 2013

CME

MDS Research Criteria for Prodromal Parkinson's Disease

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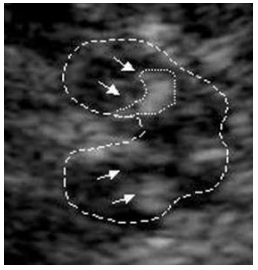
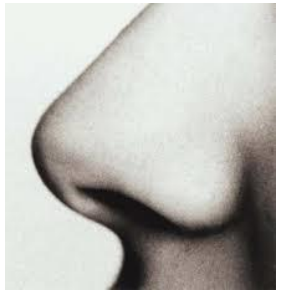
Risk markers		
Male sex	1.2 (male)	0.8 (female
Regular pesticide exposure	1.5	n/a
Occupational solvent exposure	1.5	n/a
Nonuse of caffeine	1.35	0.88
Smoking		
Current	n/a	0.45
Never	1.25	n/a
Former	n/a	0.8
Sibling had PD with age onset <50	7.5	n/a
or		
Any other first-degree relative with PD	2.5	n/a
or		
Known gene mutation	see Supporting Table II	n/a
SN hyperechogenicity	4.7	0.45
Prodromal markers		
PSG-proven RBD	130	0.62
or		
Positive RBD screen questionnaire with >80% specificity	2.3	0.76
Dopaminergic PET/SPECT clearly abnormal (e.g., <65% normal, 2 SDs below mean)	40	0.65
Possible subthreshold parkinsonism (UPDRS >3 excluding action tremor)	10	0.70
or		
Abnormal quantitative motor testing	3.5	0.60
Olfactory loss	4.0	0.43
Constipation	2.2	0.80
Excessive daytime somnolence	2.2	0.88
Symptomatic hypotension	2.1	0.87
Severe erectile dysfunction	2.0	0.90
Urinary dysfunction	1.9	0.90
Depression (± anxiety)	1.8	0.85



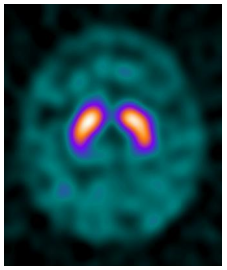
SN hyperechogenicity



hyposmia

Depression
and anxiety

Autonomic dysfunction
And constipation



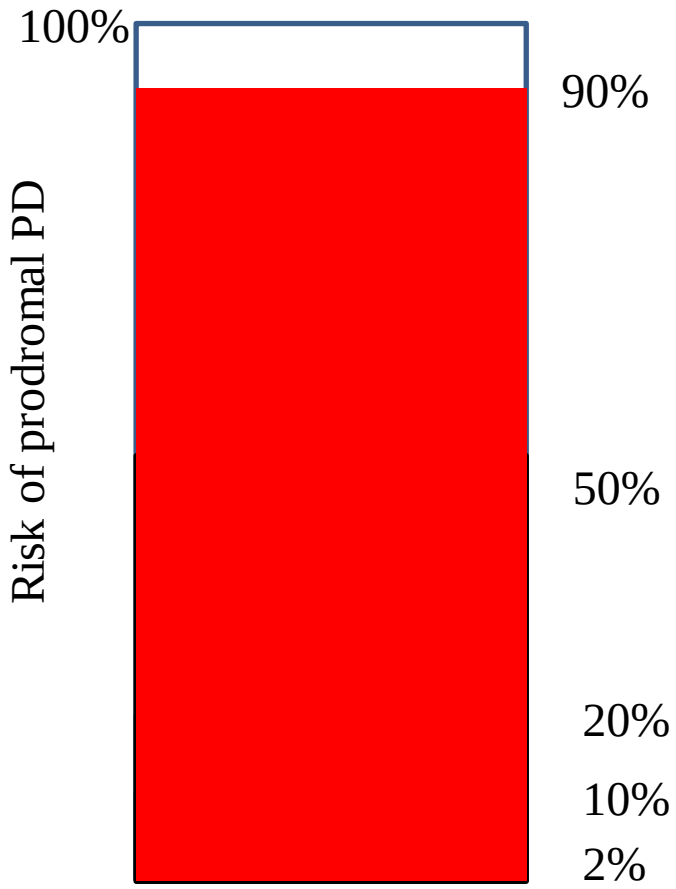
Dopaminergic
dysfunction

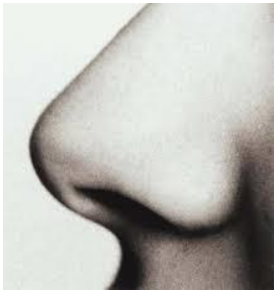
Rem behavioral disorders

Visual alterations and
cognitive impairment

Prodromal PD symptoms and markers

Prodromal PD criteria calculation





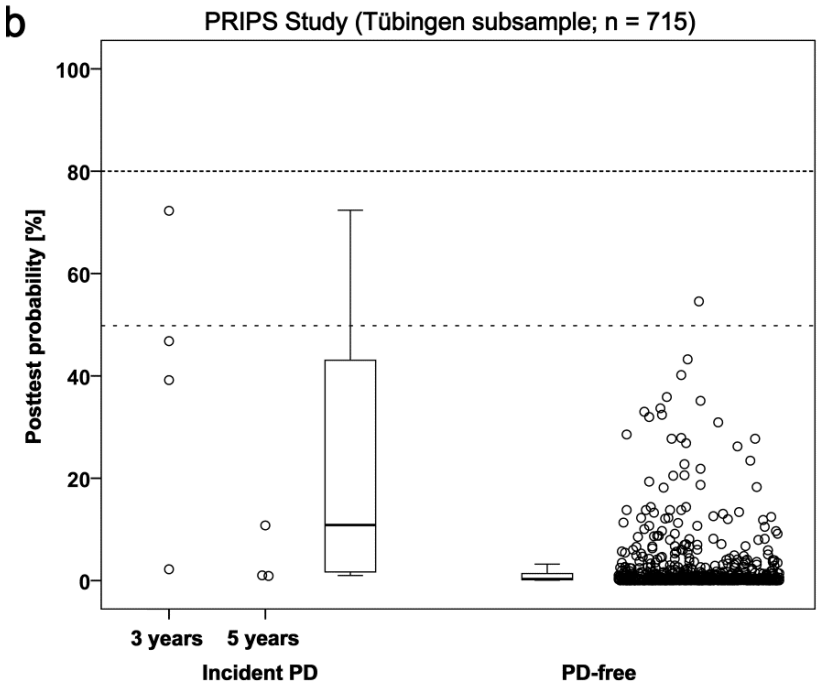
Male subject, 70 years old

RESEARCH ARTICLE

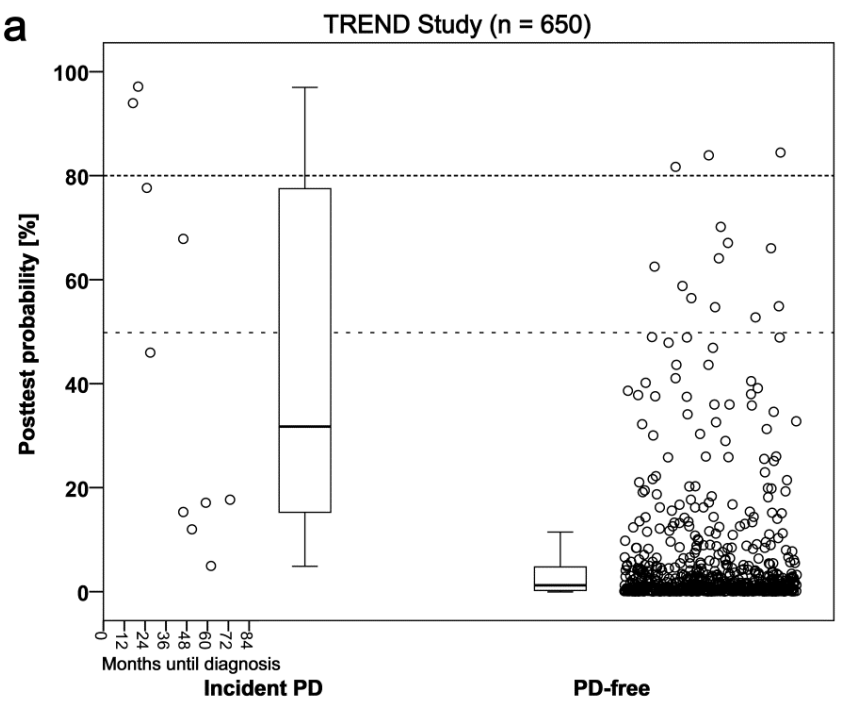
Application of the Movement Disorder Society Prodromal Parkinson's Disease Research Criteria in 2 Independent Prospective Cohorts

Andrea Pilotto, MD,[1,2] Sebastian Heinzel, PhD,[1,3] Ulrike Suenkel, MD,[1*] Stefanie Lerche, PhD,[1] Kathrin Brockmann, MD,[1] Benjamin Roeben, MD,[1] Eva Schaeffer, MD,[3] Isabel Wurster, MD,[1] Rezzak Yilmaz, MD,[1] Inga Liepelt-Scarfone, PhD,[1,4] Anna-Katharina von Thaler, PhD,[1] Florian G. Metzger, MD,[5] Gerhard W. Eschweiler, MD,[5] Ron B. Postuma, MSc, MD,[6] Walter Maetzler, MD,[1,3] and Daniela Berg, MD[1,3*]

Population-based study

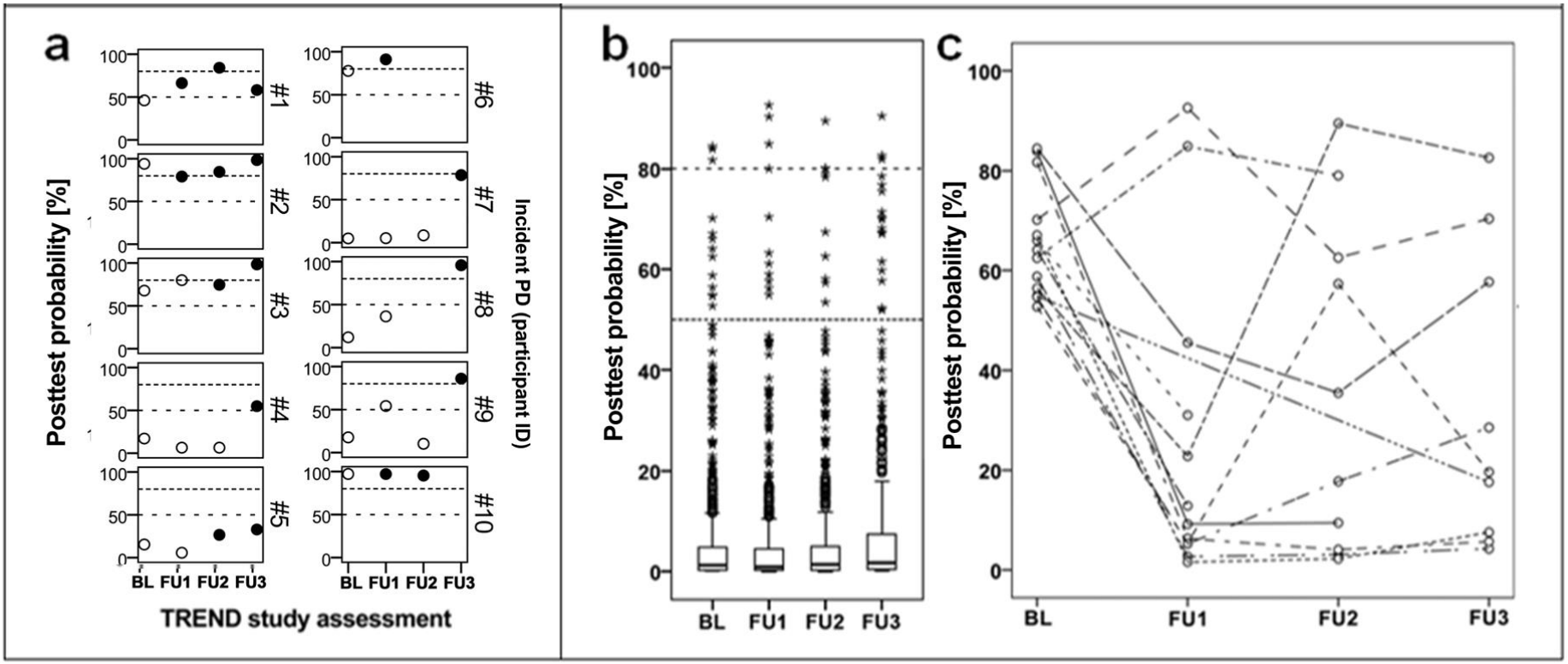


Enriched-cohort



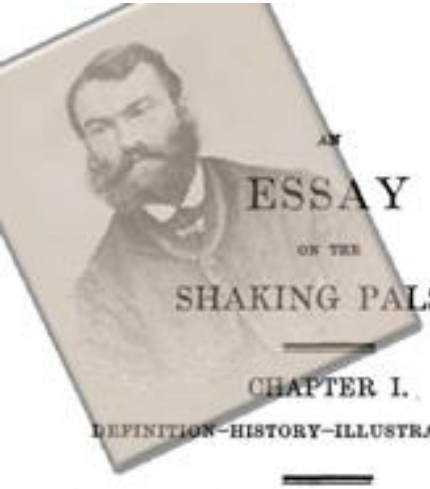
Incident PD

PD-free individuals



SN hyperechogenicity the only marker associated with PD in both cohorts (p=0.004)

Pilotto et al. 2017



AN ESSAY ON THE SHAKING PALSY.

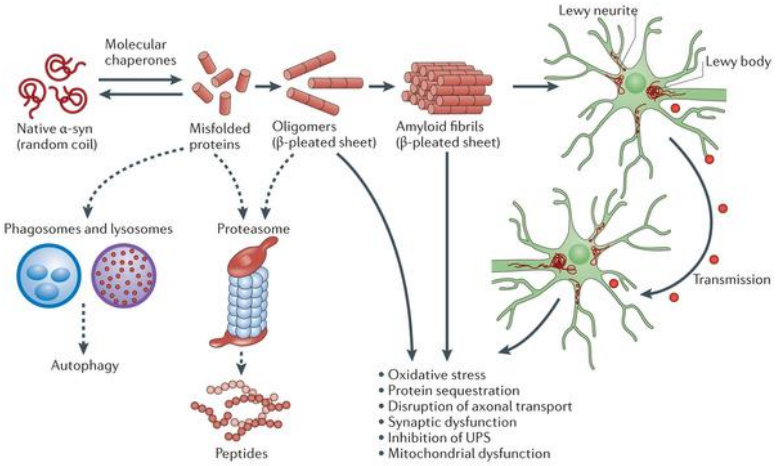
CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

The term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-

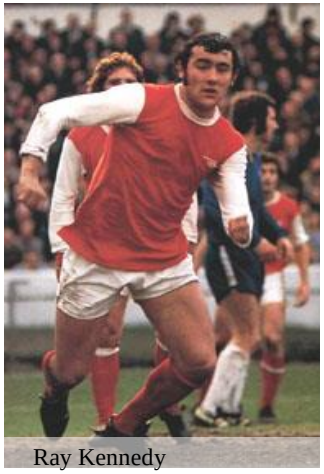


Novel technologies in TCS and prodromal neurodegeneration

Subthreshold parkinsonism

Motor Signs in the Prodromal Phase of Parkinson's Disease

Walter Maetzler, MD[1,2*] and Jeffrey M. Hausdorff, PhD[3,4,5]

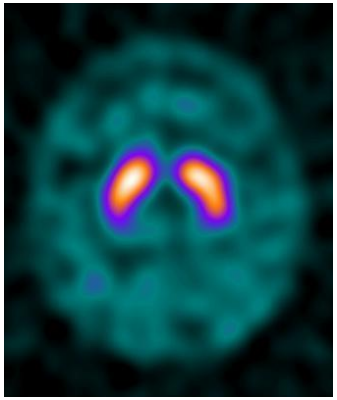


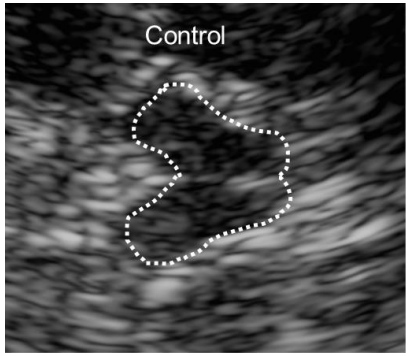
Ray Kennedy

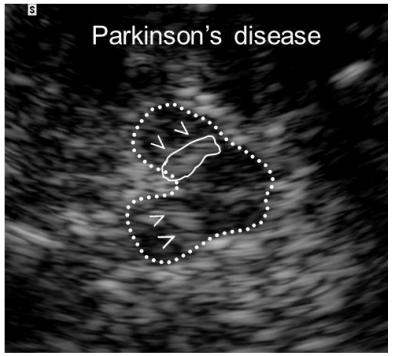
RESEARCH ARTICLE

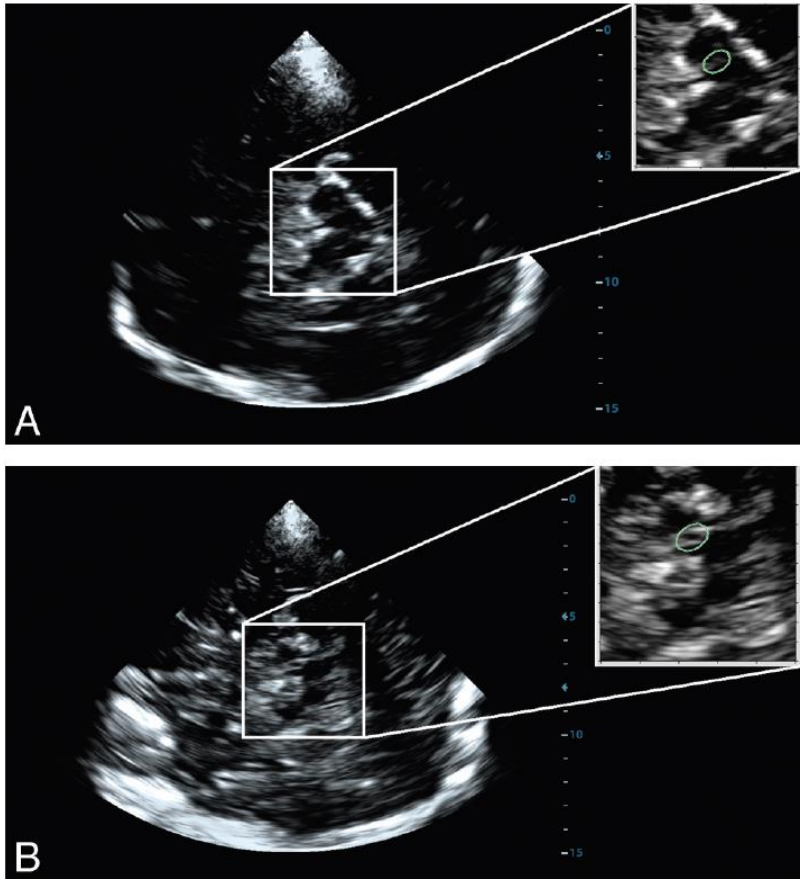
Arm Swing as a Potential New Prodromal Marker of Parkinson's Disease

Imaging markers









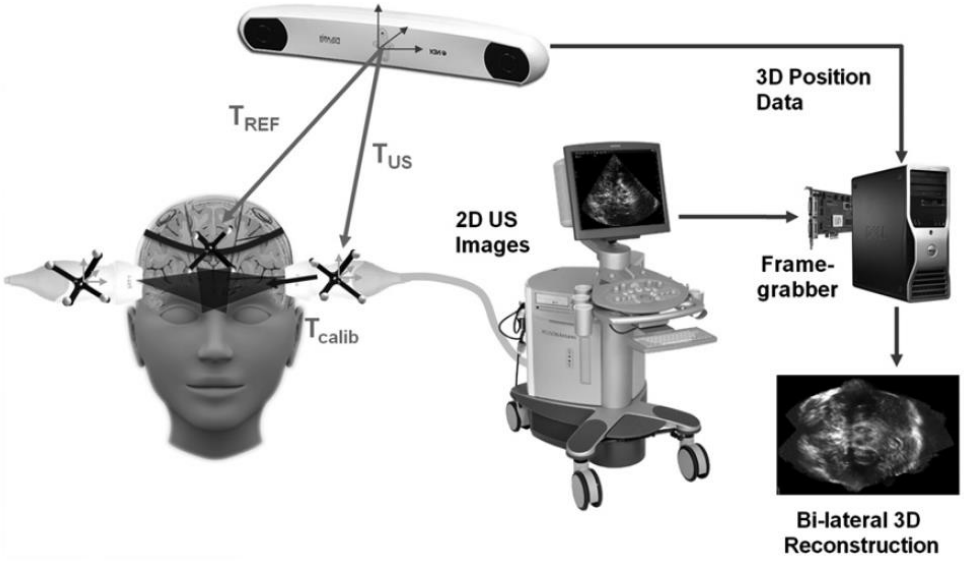
Skoloudik 2014 AJNR

- active contour algorithms
- 3D SN detection based

(random forests vs principal component analyses)

still dependent on:
- image's quality
- operator's skills

Novel technologies and methods



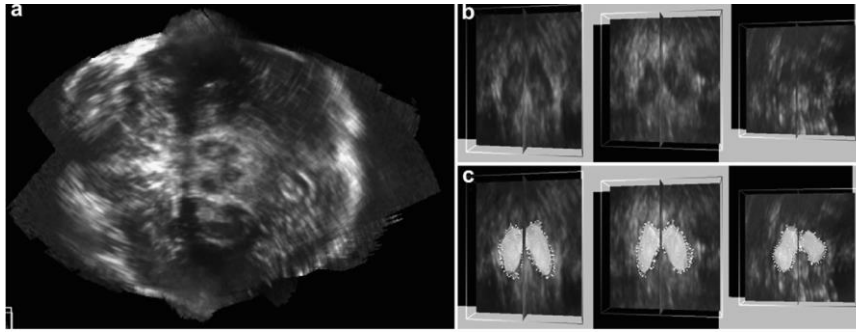
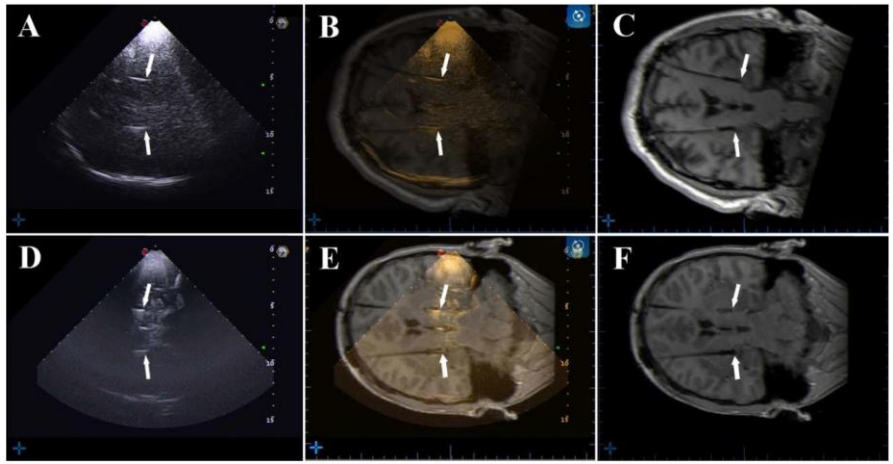


Plate et al. Ultras Med 2012

Magnetic Resonance-Transcranial Ultrasound Fusion Imaging: A Novel Tool for Brain Electrode Location

Uwe Walter, MD,[1*] Jan-Uwe Müller, MD,[2] Johannes Rösche, MD,[1] Michael Kirsch, MD,[3] Annette Grossmann, MD,[4] Reiner Benecke, MD,[1] Matthias Wittstock, MD,[1†] and Alexander Wolters, MD[1†]



SN+ is present in 90% of PD patients

TCS can be used in differential diagnosis of movement disorders

TCS can be used for differential diagnosis of dementia

TCS can identify prodromal neurodegeneration

Advantages:	easy to apply quick to perform (dyskinetic, agitated) cheap
Disadvantages:	dependent on investigator/ultrasound system insufficient bone window in about 10-15%

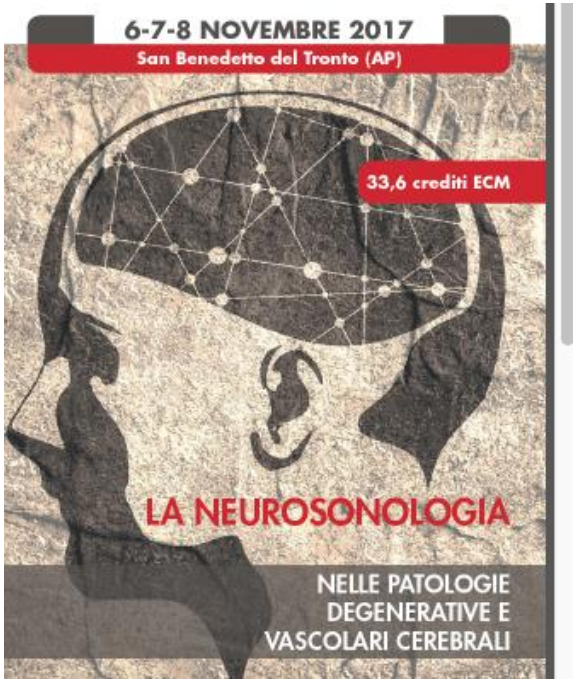
Prof. Alessandro Padovani

Prof. Barbara Borroni

Neurology Unit

Department of Clinical and Experimental Sciences

University of Brescia, Italy



Prof. Daniela Berg

Department of Neurodegeneration

Hertie Institut for Clinical Bain Research,

DZNE German Center for Neurodeenerative disorders

University of Tuebingen, Germany