I DISTURBI PSICO-COMPORTAMENTALI
NEL QUADRO CLINICO DELLE DEMENZE

SEMINARI DEL MONDINO | 2021

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Behavioral and psychological symptoms of dementia (BPSD)

- Often referred to as “non-cognitive symptoms of dementia”
- High prevalence: affect 98% of individuals with dementia
- The most critical and distressful aspects referred to by the caregiver
- Bad prognosis: elevated disability, institutionalization, and death
- Inverse correlation between BPSD and cognitive/functional outcomes
- Management strategies for the BPSD
BPSD: new perspectives

- BPSD show good sensitivity and specificity, such to be included as core or support diagnostic criteria:
  - visual hallucinations and REM behavioral disorders in LBD (McKeith et al., 2017)
  - disinhibition, apathy, aberrant motor behavior and eating disorders in FTD (Rascovsky et al., 2011)

- BPSD (i.e. apathy) show in aMCI a sevenfold risk of AD conversion (Palmer et al., 2010)
Behavioral and psychological symptoms of dementia (BPSD)

- BPSD prevalence and phenomenology
- BPSD clinical evaluation with the NPI scale
- Diagnostic biomarkers of BPSD
  - Neuroimaging
  - CSF
- Prognostic biomarkers of BPSD
- Conclusion remarks
bvFTD diagnostic criteria

I. Neurodegenerative disease
   The following symptom must be present to meet criteria for bvFTD
   A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD
   Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertaintment requires that symptoms be persistent or recurrent, rather than single or rare events.
   A. Early* behavioural disinhibition (one of the following symptoms (A.1–A.3) must be present):
      A.1. Socially inappropriate behaviour
      A.2. Loss of manners or decorum
      A.3. Impulsive, rash or careless actions
   B. Early apathy or inertia (one of the following symptoms (B.1–B.2) must be present):
      B.1. Apathy
      B.2. Inertia
   C. Early loss of sympathy or empathy (one of the following symptoms (C.1–C.2) must be present):
      C.1. Diminished response to other people's needs and feelings
      C.2. Diminished social interest, interrelatedness or personal warmth
   D. Early perseverative, stereotyped or compulsive/ritualistic behaviours (one of the following):
      D.1. Simple repetitive movements
      D.2. Complex, compulsive or ritualistic behaviours
      D.3. Stereotyping of speech
   E. Hyperorality and dietary changes (one of the following symptoms (E.1–E.3) must be present):
      E.1. Abnormal food preferences
      E.2. Binge eating, increased consumption of alcohol or cigarettes
      E.3. Oral exploration or consumption of inedible objects
   F. Neuropsychological profile: executive generation deficits with relative sparing of memory symptoms (F.1–F.3) must be present:
      F.1. Deficits in executive tasks
      F.2. Relative sparing of episodic memory
      F.3. Relative sparing of visuospatial skills

III. Probable bvFTD
   All of the following symptoms (A–C) must be present to meet criteria.
   A. Meets criteria for possible bvFTD
   B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
   C. Imaging results consistent with bvFTD (one of the following (C.1–C.2) must be present):
      C.1. Frontal and/or anterior temporal atrophy on MRI or CT
      C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology
   Criterion A and either criterion B or C must be present to meet criteria.
   A. Meets criteria for possible or probable bvFTD
   B. Histopathological evidence of FTLD on biopsy or at post-mortem
   C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD
   Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.
   A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
   B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
   C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

K. Rascovsky et al., 2011
**DLB diagnostic criteria**

***Essential*** for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment stages but is usually evident with progression. Deficits and visuospatial ability may be especially prominent.

**Core clinical features** *(The first 3 typically occur early)*
- Fluctuating cognition with pronounced variations in affect.
- Recurrent visual hallucinations that are typically well formed.
- REM sleep behavior disorder, which may precede cognition impairment.
- One or more spontaneous cardinal features of parkinsonism: slowness of movement and decrement in amplitude of arm swing.

**Supportive clinical features**
- Severe sensitivity to antipsychotic agents; postural instability; transient episodes of unresponsiveness; severe autonomic dysfunction: orthostatic hypotension, urinary incontinence, hypersalivation, dysphagia, and dysphonia.
- Systematized delusions: apathy, anxiety, and depression.

**Indicative biomarkers**
- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
- Abnormal (low uptake) 123Iodine-MIBG myocardial scintigraphy.
- Polysomnographic confirmation of REM sleep without atonia.

**Supportive biomarkers**
- Relative preservation of medial temporal lobe structures on CT/MRI scan.
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity + the cingulate island sign on FDG-PET imaging.
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

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**Probable DLB** can be diagnosed if:
- a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or
- b. Only one core clinical feature is present, but with one or more indicative biomarkers.

**Probable DLB** should not be diagnosed on the basis of biomarkers alone.

**Possible DLB** can be diagnosed if:
- a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or
- b. One or more indicative biomarkers is present but there are no core clinical features.

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I. McKeith et al., 2017
AD diagnostic criteria

Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype
- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type, based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)
- Decreased Aβ42, together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP)

Exclusion criteria for typical AD
- History
  - Sudden onset
  - Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioural changes
- Clinical features
  - Focal neurological features
  - Early extrapyramidal signs
  - Early hallucinations
  - Cognitive fluctuations

Other medical conditions severe enough to account for memory and related symptoms
- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations
- MRI FLAIR or T2 signal changes in the medial temporal lobe that are consistent with infections or vascular insults

Panel 2: IWG-2 criteria for atypical AD (A plus B at any stage)

A Specific clinical phenotype (one of the following)
- Posterior variant of AD (including)
  - An occipitotemporal variant defined by the presence of an early, predominant, and progressive impairment of visuoperceptive functions or of visual identification of objects, symbols, words, or faces
  - A biparietal variant defined by the presence of early, predominant, and progressive difficulty with visuospatial function, features of Gerstmann syndrome, of Balint syndrome, limb apraxia, or neglect

B In-vivo evidence of Alzheimer’s pathology (one of the following)
- Decreased Aβ42, together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- Alzheimer’s disease autosomal dominant mutation present (in PSEN1, PSEN2, or APP)

Exclusion criteria for atypical AD
- History
  - Sudden onset
  - Early and prevalent episodic memory disorders

Other medical conditions severe enough to account for related symptoms
- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, or metabolic disorders

AD=Alzheimer’s disease. *Additional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions)."
BPSD prevalence and phenomenology

BPSD prevalence and phenomenology
Psychothnic symptoms: delusions

Psychothnic symptoms:

• Delusions
  Content-specific autobiographical delusions:
    • **Persecutory delusions**
    • **Misidentification delusions**
  • Hallucinations

[Table with options for delusions:
  - Fear of harm
  - Fear of theft
  - Spousal affair
  - Phantom boarder
  - Spouse imposter
  - House not home
  - Fear of abandonment
  - Talks to TV, etc.
  - Other]]
1. Il/la paziente pensa mai che la propria casa non sia la sua casa?
2. Il/la paziente è mai convinto/a che altre persone (ad esempio il coniuge o uno dei figli) siano state rimpiazzate da qualcuno identico o quasi (che in realtà è un “impostore”)?
3. Il/la paziente è mai convinto/a che oggetti (o animali) siano stati rimpiazzati da doppioni identici o quasi, che però non è l’oggetto originale?
4. Il/la paziente pensa mai che persone sconosciute nascondano in realtà una persona a lui/lei nota, che si è mascherata per sfuggirgli?
5. Il/la paziente è mai convinto che esistano due luoghi fisici uguagli (ad es. la propria casa o la propria città) che però si trovano in posti diversi (ad esempio che ci sono due case identiche in vie diverse della stessa città? O due città con lo stesso nome magari nella stessa regione ma in due luoghi diversi?)
6. Il/la paziente pensa mai che certe persone si trasformino in altre sotto i suoi occhi?
7. Il/la paziente ha mai affermato che esistono dei doppioni di sé stesso (che magari vivono altrove)?
8. Il/la paziente è mai convinto che la propria immagine riflessa nello specchio rappresenti una persona che lo perseguita?
9. Il/la paziente sdoppia mai persone o oggetti (per esempio le parla di lei come se stesse parlando ad un’altra persona)?
10. Il/la paziente pensa mai che le immagini della televisione o delle riviste siano realmente presenti in casa?
11. Il/la paziente crede mai di essere morto, o di non esistere, o che i suoi organi siano in disfacimento o si stiano disgregando?

The prevalence of Misidentification Delusions in neurodegenerative diseases

Tot 190 pz
MD in 33.3% (MD-NPI), in **36.0%** (MDQ)
MD in: **34.2%** AD
**52.4%** DLB
any FTD

AD: misidentification of the house (28.1%)
splitting of people (8.9%)
reduplicative paramnesia (7.5%)

DLB: misidentification of the house (47.6%)
Capgras for people (33.3%)
reduplicative paramnesia (23.8%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AD (n = 146)</th>
<th>DLB (n = 21)</th>
<th>FTD (n = 6)</th>
<th>VaD + Mix (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misidentification of the house</td>
<td>41 (28.1%)</td>
<td>10 (47.6%)</td>
<td>—</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td>Capgras/people</td>
<td>5 (3.4%)</td>
<td>7 (33.3%)</td>
<td>—</td>
<td>4 (30.8%)</td>
</tr>
<tr>
<td>Capgras/objects &amp; animals</td>
<td>6 (4.1%)</td>
<td>2 (9.5%)</td>
<td>—</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>Fregoli</td>
<td>1 (0.7%)</td>
<td>2 (9.5%)</td>
<td>—</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Reduplicative paramnesia</td>
<td>11 (7.5%)</td>
<td>3 (14.3%)</td>
<td>—</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>Internetamorphosis</td>
<td>2 (1.4%)</td>
<td>3 (14.3%)</td>
<td>—</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>Syndrome of subjective doubles</td>
<td>—</td>
<td>1 (4.8%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mirrored self-misidentification</td>
<td>7 (4.8%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Splitting of people</td>
<td>13 (8.9%)</td>
<td>4 (19.0%)</td>
<td>—</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>Television</td>
<td>9 (6.2%)</td>
<td>4 (19.0%)</td>
<td>—</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Cotard</td>
<td>1 (0.7%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>50 (34.2%)</td>
<td>11 (52.4%)</td>
<td>—</td>
<td>6 (46.1%)</td>
</tr>
<tr>
<td>1-2 MD</td>
<td>39 (26.7%)</td>
<td>5 (23.8%)</td>
<td>—</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>3-4 MD</td>
<td>11 (7.5%)</td>
<td>4 (19.0%)</td>
<td>—</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>5-6 MD</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>&gt; 6 MD</td>
<td>—</td>
<td>2 (9.5%)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Capgras delusion

J. Capgras & J. Reboul-Lachaud

- Descrivono una paziente che riferisce che membri della sua famiglia e del suo entourage sono stati rimpiazzati da doppi identici

- Precedenti descrizioni
  - Magnan, 1893
  - Bessière, 1913

- Eponimo “sindrome di Capgras” coniato da Levy-Valensi nel 1929

Il soggetto ritiene che una persona, solitamente a lui familiare, sia stata rimpiazzata da una copia esatta (fisicamente, non psicologicamente)

Errore specifico di identificazione che coinvolge una persona con la quale il soggetto ha spesso forti legami emotivi e nei confronti della quale sono riconoscibili marcati elementi di ambivalenza al momento dell’esordio

La convinzione ha tutte le caratteristiche del delirio
Examples of Capgras syndrome in neurodegenerative diseases

• Patient believes his wife has been replaced by an impostor
• Patient believes his daughter has been replaced by his dead sister
• Patient believes her husband is a lady or a stranger living in the house
• Patient will look at his wife and ask: “where is my wife?”
• Patient believes there are six people including his wife all named Shirley
• Patient said “I’m looking for Bob my husband, not him Bob”
• Patient believes there are two daughters and two sons who look alike
• Patient said “someone homosexual is masquerading as my wife”

KA Josephs. Arch Neurol 2007; 64: 1762-1766
Il doppio in letteratura

- E. A. Poe
  William Wilson
  La camera oscura
- G. de Maupassant
  Le Horla
- L. Pirandello
  Il fu Mattia Pascal
  Uno, nessuno e centomila
- I. Calvino
  Il Visconte dimezzato
- R. L. Stevenson
  Lo strano caso del dr. Jeckyll e di Mr. Hyde
- F. Kafka
  La metamorfosi

Dostoevskij
- I demoni (1871):
  Nikolaj Vsevolodovič Stavrogin (il protagonista) non viene riconosciuto dalla moglie (Marja Timofejevna Lebjadkin): “tu sei come lui, gli assomigli molto, ma mio marito è un falcone e un principe mentre tu sei un gufo e un bottegaio”)

Capgras
- Il sosia (1864):
  Jakov Petrovich Goljadkin dopo essere stato vergognosamente cacciato da una festa presso il suo palazzo, incontra una curiosa figura che non solo gli somiglia in maniera impressionante, ma porta anche il suo stesso nome, oltre che aver vissuto la sua stessa storia e provenire dal suo stesso paese.

Doppi soggettivi
Capgras delusion: a window on face recognition

(a) Visual impairment in prosopagnosia
(b) Visual impairment in Capgras delusion

Trends Cogn Sci 2001

HD Ellis and MB Lewis. Trends Cogn Sci 2001
Patients presenting with neuropsychiatric symptoms **mimicking** bvFTD, but **lacking:**
- frontotemporal atrophy/hypometabolism on **neuroimaging** and
- **not evolving** to dementia over at least 3 years after symptom onset → do not satisfy the diagnostic criteria for probable bvFTD

“phenocopy” of FTD (phFTD)
“non-progressive” FTD
“benign” FTD
“slowly progressive” FTD
“indolent” FTD

<table>
<thead>
<tr>
<th>bvFTD</th>
<th>phFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male predominence</td>
</tr>
<tr>
<td>Family history for dementia</td>
<td>Rate</td>
</tr>
<tr>
<td>Behavioral symptoms</td>
<td>Frontal behavior</td>
</tr>
<tr>
<td>Global cognitive efficiency</td>
<td>Generally preserved</td>
</tr>
<tr>
<td>Executive function</td>
<td>Normal to mild impairment</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>Normal</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>No impairment</td>
</tr>
<tr>
<td>MRI</td>
<td>Normal to minimal changes</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Usually normal</td>
</tr>
</tbody>
</table>

ES Valente. Alzheimer’s Research & Therapy 2019;11:30

**slow neurodegenerative process** vs **late-onset psychiatric disorder**
### Overlap of bvFTD and Psychiatric Conditions

<table>
<thead>
<tr>
<th>bvFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural disturbances may not be better explained by a psychiatric condition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Late-onset depression</strong></th>
<th><strong>Late-onset schizophrenia - Bipolar disorder</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy and inertia and changes in empathy</td>
<td>Psychotic features, obsessive compulsive features</td>
</tr>
<tr>
<td>depressed mood or <strong>diminished interest or pleasure in activities</strong></td>
<td>distinctive period of abnormally and persistently elevated or irritable mood in addition to:</td>
</tr>
<tr>
<td>(1) <strong>significant change in weight or appetite</strong></td>
<td>(1) inflated self-esteem or grandiosity</td>
</tr>
<tr>
<td>(2) insomnia or hypersomnia</td>
<td>(2) decreased need for sleep</td>
</tr>
<tr>
<td>(3) psychomotor agitation or retardation</td>
<td>(3) more talkative than usual or pressure to keep talking</td>
</tr>
<tr>
<td>(4) fatigue or loss of energy</td>
<td>(4) flight of ideas or racing thoughts</td>
</tr>
<tr>
<td>(5) feelings of worthlessness or guilt</td>
<td>(5) distractibility</td>
</tr>
<tr>
<td>(6) diminished concentration</td>
<td>(6) <strong>increased goal-directed activity or psychomotor agitation</strong></td>
</tr>
<tr>
<td>(7) recurrent thoughts of death or suicide</td>
<td>(7) excessive involvement in activities that have a high potential for negative consequences</td>
</tr>
</tbody>
</table>
Behavioral and psychological symptoms of dementia (BPSD)

✓ BPSD prevalence and phenomenology

✓ BPSD clinical evaluation with the NPI scale

✓ Diagnostic biomarkers of BPSD
  ✓ Neuroimaging
  ✓ CSF

✓ Prognostic biomarkers of BPSD

✓ Conclusion remarks
The neuropsychiatric inventory (NPI): development

- The NPI was developed and validated specifically for the neuropsychiatry of neurodegenerative diseases

- **Informant-based interview**
  - Screening questions
  - Frequency (1-4) and severity (1-3)

- Low rates of mood symptoms, anxiety and apathy are present in healthy elderly

- Pharmacological trials
  - 1-point worsening of the NPI → increase of 247-409$ per year in total direct costs of care

**Table 1.** Domains of the Neuropsychiatric Inventory.

<table>
<thead>
<tr>
<th>Depression</th>
<th>Delusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Irritability</td>
<td>Agitation</td>
</tr>
<tr>
<td>Elation</td>
<td>Aberrant motor disturbances</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>Appetite/eating changes</td>
</tr>
<tr>
<td>Apathy</td>
<td>Night time sleep disturbances</td>
</tr>
</tbody>
</table>

J Cummings. Journal of Geriatric Psychiatry and Neurology 2020;33(2) 73-84
Versions of the NPI

- > 40 languages

- Differences in behavioral changes in different cultures:
  - anxiety and delusions: Chinese > Caucasians
  - appetite changes and apathy: Caucasians > Chinese
  - Chinese caregivers had less distress than Caucasian caregivers to patient depression and apathy.

- Baseline scores across 7 geographic regions had substantial heterogeneity:
  - from 6.6 in Japan to 11.9 Australia/South Africa and South America/Mexico.
Challenges with the use of the NPI

**Summation score**
- The F x S approach results in asymmetric score distributions; scores of 5, 7, and 11 cannot be achieved.
  → NPI-c

**Domain-specific scales:**
- Hamilton Depression Rating Scale (HDRS)
- Cohen-Mansfield Agitation Inventory (CMAI)
- Apathy Evaluation Scale (AES)
  ...

**Domains to be re-evaluated:**
- Separate agitation/aggression
- Lack of changes in sexual demeanor and the impulse control disorders
Behavioral and psychological symptoms of dementia (BPSD)

✓ BPSD prevalence and phenomenology
✓ BPSD clinical evaluation with the NPI scale
✓ **Diagnostic biomarkers of BPSD**
  ✓ Neuroimaging
  ✓ CSF
✓ Prognostic biomarkers of BPSD
✓ Conclusion remarks
Neuroimaging correlates of BPSD in AD

- Review of morphological, perfusion and metabolic changes associated with BPSD

- Delusions, apathy and depression symptoms were particularly associated with brain changes

- **Frontal** lobe is the most involved; interestingly, for all 12 BPSD, the **anterior cingulate cortex** is affected.
Neuroimaging predictors of BPSD in AD

- Voxel-based morphometry at baseline and longitudinally at 6-month intervals NPI
- Up to 23 structures predicted the occurrence of BPSD. The frontal cortical volume was the most powerful predictor of BPSD, especially the frontal gyrus.
- The BPSD for which the most structures were involved are anxiety, depression, hallucinations, and aberrant motor behavior.
Neuroimaging lateralization of BPSD

**Left:** apathy, agitation, hallucinations, appetite disorder

**Right:** delusions, disinhibition, irritability, elation, sleep disorder

Both: depression, aberrant motor behavior, anxiety
Neuroimaging correlates of BPSD in bvFTD

A **Apathy:** medial frontal region bilaterally, including the dorsal anterior cingulate cortex and medial orbital frontal cortex, bilateral inferior frontal, bilateral anterior temporal, right dorsolateral prefrontal cortex

B **Disinhibition:** medial orbital frontal cortex, bilateral inferior frontal, bilateral anterior temporal, left dorsolateral prefrontal cortex

Neuroimaging correlates of BPSD in bvFTD

Table 1: NPI feature scores in bvFTD subtypes.

<table>
<thead>
<tr>
<th>NPI feature</th>
<th>bvFTD (n = 66)</th>
<th>bvFTD subtypes</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Temporal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dominant (n = 6)</td>
<td>parietal (n = 27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frontotemporal (n = 12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frontal</td>
<td></td>
</tr>
<tr>
<td>Total NPI-Q severity score</td>
<td>8 (4–12)</td>
<td>8 (3–19)</td>
<td>8 (3–11)</td>
</tr>
<tr>
<td>Agitation</td>
<td>24 (45)</td>
<td>3 (60)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>23 (43)</td>
<td>2 (40)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Apathy</td>
<td>43 (81)</td>
<td>3 (60)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Appetite and eating behaviours</td>
<td>35 (66)</td>
<td>4 (80)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Night-time behaviour</td>
<td>19 (37)</td>
<td>2 (40)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Delusions</td>
<td>13 (25)</td>
<td>2 (40)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Depression</td>
<td>26 (49)</td>
<td>1 (20)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>29 (55)</td>
<td>3 (60)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>19 (36)</td>
<td>0</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>4 (8)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Irritability</td>
<td>22 (42)</td>
<td>3 (60)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Aberrant motor behaviour</td>
<td>22 (42)</td>
<td>3 (60)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

Neuroimaging correlates of BPSD: cortical atrophy visual rating scales

MTA
Scheltens, 1992

PA
Koedam, 2011

GCA-F
Van der Flier and Scheltens, 2018
Neuroimaging correlates of BPSD: cortical atrophy visual rating scales

Neuroanatomical correlates of BPSD

- Unexpected additional pathology in 9/16 cases: all BPSD cases have a mix of proteopathies
- No patient without degenerative limbic lesions had BPSD
- 2 limbic lesions and absence of BPSD: isolated LTS or TDP-43 pathology
- 9 limbic lesions and BPSD: 4 (TDP-43+LTS), 4 (TDP-43+AD), 1 (LTS+AD)
- 5 absence of BPSD: no degenerative limbic lesions

The **limbic system is confirmed as a "HUB" of behavior**

The limbic co-localization of LTS and TDP-43 may underlie more severe BPSD

“Psychotic symptoms in dementia are the expression of regional rather than diffuse brain pathology affecting primarily the frontal lobe and limbic region.”

TE Poloni. AAIC 2019
CSF correlates of BPSD

**Figure 3** Relationship between CSF t-tau and NPI total score according to disease stages. Stage was defined according to MMSE score: 24–30, mild cognitive impairment; 12–23, mild-to-moderate dementia; 0–11, moderate-to-severe dementia. Correlations: stage 24–30: $R = 0.11$, $p = 0.597$; stage 12–23: $R = -0.07$, $p = 0.657$; stage 0–11: $R = -0.55$, $p = 0.083$. 

Behavioral and psychological symptoms of dementia (BPSD)

- BPSD prevalence and phenomenology
- BPSD clinical evaluation with the NPI scale
- Diagnostic biomarkers of BPSD
  - Neuroimaging
  - CSF
- Prognostic biomarkers of BPSD
- Conclusion remarks
Towards the use of prognostic biomarkers of BPSD...

### TABLE 2

|                | Estimate | Std. error | Z-value | p-value = pr(>|z|) |
|----------------|----------|------------|---------|--------------------|
| Intercept      | 4.204    | 2.144      | 1.961   | 0.050              |
| Age            | -0.053   | 0.026      | -2.018  | **0.044**          |
| Male gender    | -1.661   | 0.444      | -3.741  | **0.0002**         |
| Education      | -0.099   | 0.051      | -1.932  | 0.053              |
| MMSE           | 0.036    | 0.030      | 1.198   | 0.231              |
| t-tau          | -0.002   | 0.001      | -2.855  | **0.004**          |
| Aβ42           | -0.001   | 0.001      | -1.820  | 0.069              |
| GCA L          | -1.178   | 0.831      | -1.418  | 0.156              |
| GCA R          | 1.844    | 0.912      | 2.022   | **0.043**          |

GCA, global cortical atrophy; L, Left; MMSE, Mini-Mental State Examination; R, right.
Conclusions

- REM sleep behavior disorder
- Polysomnographic confirmation of REM sleep without atonia
- DLB
  - McKeith et al., 2017
  - Phenoconversion to PD/DLB/MSA
    - conversion rate 6.3% per year, 73.5% after 12-year (Postuma et al., 2019)
Grazie per l’attenzione!