Title Describing and assessing behavioural symptoms in amyotrophic lateral sclerosis (ALS) with and without frontotemporal dementia: a scoping review

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Abstract

Purpose of review

Alongside motor and cognitive symptoms, Amyotrophic Lateral Sclerosis (ALS) and ALS with Frontotemporal Dementia (ALSFTD) present with behavioural symptoms which can be challenging for all affected by the disease. A scoping review of studies published between 2011-2024 was conducted to present the breadth of behavioural symptoms in ALS and ALSFTD, explore how they are described and assessed, and identify patterns in the literature.

Findings

This scoping review identified 3,939 articles, with 111/3,939 meeting eligibility criteria. Most studies were from Australia (23.22%), Italy (16.94%) and the UK (14.29%); 75.67% were cross-sectional. Sample size ranged from 1-1,013, as case studies were included. Overall mean age (100/111 studies) was 61.32 (SD=4.15). Proportion of male patients (reported 102/111 studies) was 61.49%; mean disease duration (reported in 86/111 records) was 32.63 months (SD=24.72). Papers described a broad range of behavioural symptoms (465 examples), which were thematically collated into seven categories: disinhibition (27.74%), apathy (25.16%), perseverative/compulsive behaviours (17.42%), hyperorality (10.53%), loss of sympathy or empathy (8.6%), psychotic symptoms (7.74%), and loss of insight about disease and changes (2.8%). Most studies (78.37%) used validated behavioural assessments that elicited carer's perspectives.

Summary

Despite extensive evidence of behavioural symptoms in ALS, implementation of assessments and management of behavioural symptoms in clinical care remain limited. Clinicians must assess behavioural symptoms, as these can negatively affect disease prognosis, patient treatment engagement and increase family distress. . Measures capturing carers' perspectives through interviews are ideal as they can reveal anosognosia, lack of sympathy and lack of empathy.

Background

Amyotrophic Lateral Sclerosis (ALS), also referred as Motor Neurone Disease (MND), has transitioned from being solely recognized as a neuromuscular disease to being acknowledged as a neurodegenerative and multisystem condition (1). The discovery of the role of C9orf72 in people living with ALS (pwALS) in 2011 (2, 3) provided the strongest link supporting a continuum between MND and Frontotemporal Dementia (FTD).

Sharing an overlapping genetic basis, up to 50% of pwALS also present with behavioural and cognitive symptoms, with 15% fulfilling the diagnostic criteria of FTD (4). It is noteworthy that behavioural symptoms may precede the onset of ALS (5), and that many FTD patients have subclinical motor deficits (6). However, a comprehensive exploration of how behaviours are described and assessed in ALS and ALSFTD, have not been scoped to date.

Research has highlighted the psychological and emotional distress carers experience due to behavioural symptoms, often surpassing the impact of ALS's physical deficits (7, 8). Whilst the impact of behavioural symptoms on survival and treatment adherence is recognised, there is limited knowledge and training for healthcare professionals on how to manage behavioural symptoms and how to support carers in this process (9). Early identification and appropriate understanding of behavioural symptoms are critical factors to inform targeted interventions for both patients and carers. As such, the present scoping review was undertaken to provide a comprehensive overview of the assessment of behavioural symptoms in ALS/MND and MND/ALSFTD, while identifying patterns linked to clinical presentation.

Methods

Search strategy

A comprehensive literature search of published studies using the electronic databases Scopus, MEDLINE, CINAHL, PsycINFO and E-Journals was conducted. Sources from January/2011 to 5th February/2024 were searched Only studies in English were included. No additional hand and non-

academic literature searches were carried out. The search strategy included terms such as ALS, MND and behavioural changes, and included different behavioural symptoms such as apathy, disinhibition, and lack of empathy. As we aimed to explore behavioural changes within the spectrum of ALSFTD, papers focusing on FTD but also containing information on FTDALS patients were included.

Study selection

A scoping review was conducted, as this is the most appropriate method when the aims are to clarify concepts, determine knowledge gaps (10), and cover a large topic area obtaining the extent of information rather than focussing on depth (11). The six stages of a scoping study (11, 12) were followed: identifying the research question; identifying relevant studies; study selection; charting the data; collating, summarising and reporting the results; and consultation with stakeholders.

First, duplicates and papers published in other languages were removed. Following this, authors assessed study titles and excluded those clearly not about ALS, and those about ALS but with a clear focus beyond the remit of the current study. Abstracts and full texts were then assessed, excluding any in the aforementioned categories, reviews, opinion or discussion pieces, and conference abstracts and including those with data collection concerning behavioural symptoms in ALS and ALSFTD. Articles focused on personality traits, social cognition, and executive function were excluded. Two reviewers assessed each article for inclusion. Authors met regularly to discuss inclusion criteria and to work through aspects of uncertainty.

Charting data

A charting form including the following categories was developed: sample size, sex, age, length of symptoms, diagnostic criteria, ALS phenotype, country where data were collected, type of study, which behavioural symptoms were investigated or present, how behaviour symptoms were measured, and who reported them. All authors extracted data from the included studies; extraction

was checked by another author for a subset of articles. Uncertainties regarding extraction were discussed within the team and decisions made as to the boundaries of data required.

Collating data

Extracted data on sample size, age, sex, disease duration, country, and study design were collated and analysed numerically. Where means were reported they were collated; reported medians were in the minority and therefore not collated. Data on behavioural symptoms were collated thematically, grouping similar items under broader headings to portray the range and breadth of categorisations in the literature.

Consultation

The authors consulted with four stakeholders: one current and one former family carer of a person living with ALSFTD, and two specialist ALS healthcare professionals (HCPs), via online meetings, to gain external insights on the provisional findings.

Results

Which studies were included in this scoping review?

A PRISMA flow diagram (13) illustrates the study selection process (Supplementary Figure 1). The search retrieved 3,939 studies; from these, 111 eligible studies were included for analysis.

What were the characteristics of the included studies?

Study and participant characteristics are presented (Table 1). 75.67% studies were cross-sectional, 5.41% were longitudinal, 11.71% were case reports, 6.31% retrospective clinical cases and one record (0.90%) was a PhD dissertation. Interestingly, most studies originated in Australia (23.22%) and Italy (16.94%), representing approximately 40% of all studies included.

It appears that all studies included had a quantitative approach; we could not identify studies investigating behavioural symptoms that employed a qualitative methodology.

How were behavioural symptoms identified?

Most studies (83.78%) used a validated clinical scale (Table 2). 17.11% studies employed the Edinburgh Cognitive and Behavioural ALS Screen (ECAS (14)), 16.21% used the Cambridge Behavioural Inventory-Revised (CBI-R (15)) and 13.51% administered the Frontal Systems Behavior Scale™ (FrSBe (16)), representing almost half of all papers included (46.84%). The great majority of studies utilised assessments that involved the carer's perspectives (78.37%), e.g., family members, either via an assessment completed by them, or through interviews.

What was the breadth of behavioural symptoms identified?

Collating the data revealed a broad range of behavioural symptoms, which were described in detail, particularly when medical records had been examined, or case reports were published. This extensive list of behaviours was thematically grouped in seven categories (Figure 1): disinhibition, apathy, perseverative/compulsive behaviours, hyperorality, loss of sympathy or empathy, psychotic symptoms, and loss of insight about disease and changes. Under each category, a breadth of symptoms pertaining to that category were identified. Figure 2 shows a diagram of behavioural symptoms categories (n=7), the behaviours feeding into each category, and the thematic links between behaviours.

The most frequently behavioural symptoms reported in the included studies were categorised under disinhibition (n=129), apathy (n=117), and perseverative/compulsive behaviours (n=81) (Figure 1). Not surprisingly, these domains were also commonly included in most assessments or screening tools. Apathy (n=117), while investigated frequently, appeared to be linked to fewer related behaviours in comparison to disinhibition and perseverative/compulsive behaviours.

What did stakeholders think of our findings?

Stakeholder consultation revealed overall agreement in the proposed seven categories, except for one, which initially was called ‘sexual dysfunction’ and combined both increased and decreased interest in sex. Stakeholders felt that it was important to include ‘increased interest’ in the disinhibition category, while ‘decreased interest’ was felt to fit more appropriately within the apathy category.

‘Agitation’ was considered to be a broad and vague term, which would benefit from a review. Agitated behaviour could emerge from restlessness, anxiety or aggression; each underpinning reason would need different strategies for management, and as such, stakeholders thought better delineation of the term was needed. Therefore, agitation was not included in any category. ‘Substance abuse’ was also felt to be an imprecise term; for example, it could imply legal or illegal substances; however, the group felt that it could still fit under disinhibition.

Stakeholders also highlighted that some behavioural symptoms crossed categorical boundaries, and their reflections were included in the thematic links (lines) included in Figure 2. In their experience, for example, people living with ALSFTD may ‘gorge on food’, which could be both a symptom related to hyperorality as well as lack of insight into the disease, i.e., not understanding that they have swallowing issues and it is dangerous to eat too fast. Similarly, stakeholders pointed out that people living with ALSFTD can fluctuate between extremes of related behaviours. For example, they can present with self-neglect one day and try to go out in their pyjamas, while the next day they may overdress for an occasion.

Finally, stakeholders pointed out that some symptoms may be difficult to be noticed due to the marked motor deficits present in ALS, for example, apathy may be masked behind physical deficits - or physical deficits may prevent behavioural symptoms from occurring, ‘even if he wanted to be violent, he couldn’t be [because he has no strength in his limbs]’.

Discussion

The present scoping review revealed that a broad range of behavioural symptoms have been reported in people diagnosed with ALS or ALSFTD between 2011 and 2024. Although apathy is widely recognised as the most prominent behavioural symptom in ALS, this review show that disinhibition and perseverative/compulsive behaviours are very frequently reported. Included studies had more examples of disinhibited behaviour than apathy, both in terms of number of times reported in studies, as well as their scope, as illustrated in Figure 2. Importantly, this review also demonstrated the thematic links between behavioural symptoms, which are currently assessed in individual categories, when in reality they are interlinked between categories, e.g., examples of behavioural symptoms described under *hyperorality* can link with *disinhibition* and *perseverative behaviours*.

The range of behavioural symptoms identified in this review can be mapped well against the current diagnostic criteria for behavioural variant frontotemporal dementia (17) – disinhibition; apathy; loss of sympathy or empathy; perseverative, stereotyped behaviour; hyperorality - except for psychotic symptoms. Delusions and hallucinations were mentioned in approximately 32% of included studies and can be very distressing to families. Here, the role of the C9orf72 mutation is clearly relevant in the review period, as it has been associated with presence of psychotic symptoms, in particular in ALSFTD/FTDALS (18, 19).

Research studies have often reported that apathy is the most common behavioural symptom in ALS (20) and ALSFTD (21). However, this review shows that examples of disinhibited behaviours are more common, and likely lead to great concern – as most families do not receive information about 'difficult behaviours' as symptoms of ALS (22, 23). To complicate matters, it appears that patients show some insight into their apathy, but not their disinhibited behaviours (24). Nevertheless, these symptoms can co-occur, as shown in this review.

The negative impact of behavioural symptoms is not limited to families; HCPs also report anxiety in assessing for behavioural symptoms as they feel unprepared to support families when such non-motor symptoms are identified (25). Behavioural symptoms are very common and yet they do not feature in the most known ALS diagnostic criteria. Nevertheless, new initiatives have been identified: a recent feasibility study tested training modules on behavioural symptoms in ALS (22), which increased knowledge and was very well received by HCPs (25). Furthermore, the complexity and interconnectedness between behavioural symptoms in ALS and ALSFTD underscores the necessity of multidisciplinary teams working collaboratively to address behavioural symptoms as a team – not as a responsibility of a single professional, e.g., a psychologist.

The range of assessments identified in this review clearly map the progression of the scientific community's understanding of behavioural symptoms in the past 15 years. Assessments originally developed for frontotemporal dementia and brain injury were used quite extensively in studies published during the first half of this review period (2011-2017). However, in the latter half of the selected time period, there was a noticeable increase in the use of MND/ALS specific tools (e.g., ECAS), while also marking the publication of the revised Strong criteria (4). Australia, Italy, and the UK emerged as hotspots of research into behavioural symptoms in ALS. Of note, during the eligibility assessment stage (Supplementary Figure 1), many articles reported investigating cognitive and behavioural symptoms. At close inspection, these papers focused on cognitive symptoms only and had to be excluded from the review (26). For instance, removed studies reported use of the ECAS (27, 28), but only reported partial scores. This seems to suggest that cognitive deficits are more commonly assessed than behavioural symptoms; this is of great concern given that behavioural symptoms impact disease management (9), strongly contribute to carer burden and distress in ALS (23, 29, 30) and require HCP support (25).

It can be difficult to identify behavioural symptoms in people with ALS and ALSFTD, since patients might not have complete insight into the changes they are going through. Moreover, symptoms may not occur during an allocated healthcare appointment, and HCPs do not know how the person

behaves outside of the consultation/appointment slot. Behavioural symptoms are usually observed and difficult to 'test', and as such, the ability to identify those symptoms relies on professionals' training and family members' responses in interviews. In this review, many studies used interviews with carers to assess behavioural symptoms of the person living with ALS/ALSFTD, such as the ALS Cognitive Behavioral Screen (ALS-CBS) (31) and ECAS (14). When anosognosia may be present, interviews with carers are essential. Additionally, given the limited public knowledge that ALS also presents with behavioural symptoms, carers may not voluntarily discuss symptoms if not prompted by HCPs about them (32). Standardised assessments and interviews offer an opportunity for carers to explore and recognise these symptoms, understand them as part of ALS and work with the multidisciplinary team in identifying best ways to manage these changes (32). This collaborative approach is crucial for accurately identifying and addressing behavioural symptoms.

Related to the above, the stakeholder consultation meetings elicited further perspectives on the preliminary findings of the review, which revealed several insightful observations, interrogated the initial thematic analysis and added validation of the results. This consultation stage adds strength to a scoping review. Stakeholders also emphasised the linkages between behavioural symptoms, which are currently described and quantified in isolation in assessments. This stakeholder contribution resonates well with the lack of studies utilising a qualitative methodology, which would have potentially revealed more vivid descriptions of behavioural symptoms.

This review highlighted the limited research of psychotic symptoms within this population. Whether this scarcity is attributed to the low prevalence of psychiatric symptoms, or simply reflects the lack of studies, warrants further attention and research. Notably, published literature has suggested the possible relation between ALS and psychiatric disorders, such as schizophrenia (33, 34).

Conclusion

While apathy is well acknowledged as the most common behavioural symptoms in ALS and ALSFTD, this scoping review has identified a wide range of behavioural symptoms in these patient groups. Disinhibition and perseverative/compulsive behaviours, in particular, were frequently reported

across studies, and yet they are generally under-recognised in clinical practice. The breadth of behavioural symptoms in ALS needs to be addressed in clinical practice through routine assessment, training for HCPs, and provision of specialist support for those affected by ALS and ALSFTD.

Key Points

- There is a wide gap between research evidence and clinical practice. The pervasiveness of complex behavioural symptoms in ALS and ALSFTD is evident in the literature, while current diagnostic criteria do not acknowledge these behavioural symptoms. Consequently, assessment and management behavioural symptoms in ALS clinical practice is lacking. Specialist training for HCPs is virtually absent.
- Assessments of behavioural symptoms may require inclusion of clear examples to aide their identification by all involved. Examples can upskill healthcare professionals and help families understand and accept what is happening with the patient. Qualitative studies would enhance our understanding of behavioural symptoms, allowing for carers' full description of behavioural changes observed. New assessments of behavioural symptoms need to take into account the links between behavioural symptoms, e.g., lack of insight may link with delusions.
- Disinhibition and perseverative/compulsive behaviours are very relevant in ALS and ALSFTD, potentially as relevant as apathy, highlighting a research gap and need for greater clinical awareness.

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Conflicts of interest

In the past 10 years, EM has been funded by the MND Association, the Alzheimer's Society, the NIHR Clinical Research Network East of England, the NIHR Applied Research Collaboration East of England, and MND Scotland. EM provided consultancy for LifeArc. EM is a member of the MND Association Healthcare Research Panel and NIHR DLAF committee. For the remaining authors none were declared.

Figure Titles and Legends

Figure 1: Categories of behavioural symptoms investigated across the 111 included studies; 7 categories were identified. The number in brackets refer to the number of instances that a behavioural symptom within that category was mentioned on all included articles. Larger rectangles mean greater frequency of behavioural symptoms in that category.

Figure 2: Mind map including all behavioural symptoms identified in the 111 included studies. *Note.* In this structure, each colour represents a category of behavioural symptoms, with the category label shown in white font, e.g., disinhibition, hyperorality, psychosis. Symptoms contributing to each category are clustered around the category label, in shapes of the same colour, e.g., red for

disinhibition. A category with many shapes visually demonstrates the breadth of description for that particular category. Lines represent the connection of each individual symptom to its head category. Dotted lines represent the connections between different symptom categories.

Supplementary Figure 1: PRISMA flow diagram of all included studies in this scoping review of behavioural symptoms in MND and MNDFTD (n=111).

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Table 1: Study and participant characteristics, including diagnostic criteria used.

	n	%	Mean	SD	Range min	Range max
Study characteristics						
ALS sample size	11,743	N/A	106.75	153.21	1	1,013
Participant characteristics						
Gender (n=102 studies)						
Male	6,524	61.49	59.31	88.31	0	630
Female	4,085	38.51	37.14	55.62	0	383
Age, years (n=100 studies)			61.32	4.15		
Disease duration, months (n=86 studies)			32.63	24.72		
Methodology (n=111)						
Cross-sectional						
Observational	80	72.07				
Scale validation	04	3.60				
Longitudinal	06	5.41				
Case reports	13	11.71				
Retrospective clinical cases	07	6.31				
PhD dissertation	01	0.90				
Country of data collection (n=112) *						
Australia	26	23.22				
Italy	19	16.94				
United Kingdom	16	14.29				
United States	14	12.50				
Brazil	06	5.36				
Germany	05	4.46				
China	05	4.46				
Ireland	04	3.58				
Spain	04	3.58				
Netherlands	03	2.68				
Japan	03	2.68				
France, Belgium, Switzerland, Tunisia, Pakistan, South Korea, Taiwan	01 each *07 total*	0.89 *6.25*				
Diagnostic criteria for MND, MNDFTD, and FTD (n=111)**						
El Escorial	66					
Awaji	06					
Gold Coast	03					
Gordon	02					
Pringle	01					

Turner	01
Strong (2009, 2017)	28
Rascovsky	24
Neary	07
Gorno-Tempini	02
European Federation Neurological Sciences (EFNS)	01

NB. *Country where study took place (n=112) because one study involved data collection in two different countries. **Some studies included more than one diagnostic criteria.

Table 2. Types of assessments used for detection of behavioural symptoms (n=111 studies)

Assessment *Some studies included >1 assessment.*	
Edinburgh Cognitive and Behavioural ALS Screen (ECAS)	19
Cambridge Behavioural Inventory – revised (CBI-R)	18
Frontal Systems Behavioral Scale (FrSBe)	15
Motor Neurone Disease Behavioural Instrument (MiND-B)	09
Dimensional Apathy Scale (DAS/brief DAS)	09
Neuropsychiatric Inventory (NPI/NPI-Q)	09
Frontal Behavioral Inventory (FBI/FBI-ALS)	09
ALS Cognitive Behavioral Screen (ALS-CBS)	05
Beaumont Behavioural Inventory (BBI)	04
ALS-FTD Questionnaire (ALS-FTD-Q)	03
Frontotemporal Dementia Rating Scale (FTD-FRS)	01
Apathy Evaluation Scale (AES)	01
Iowa Scales of Personality	01
Mild Behavior Impairment (MBI)	01
Bespoke assessment (not validated)	01
Retrospective chart review of medical records	03
Not stated, or not used, e.g., case report	14
Ascertainment of presence of behavioural symptoms (n=111) *Some papers included >1 type of assessment.*	
Carer/proxy interview	87
Self-report (person with MND)	16
Observation by clinician; clinician-rated	04
Not stated	17

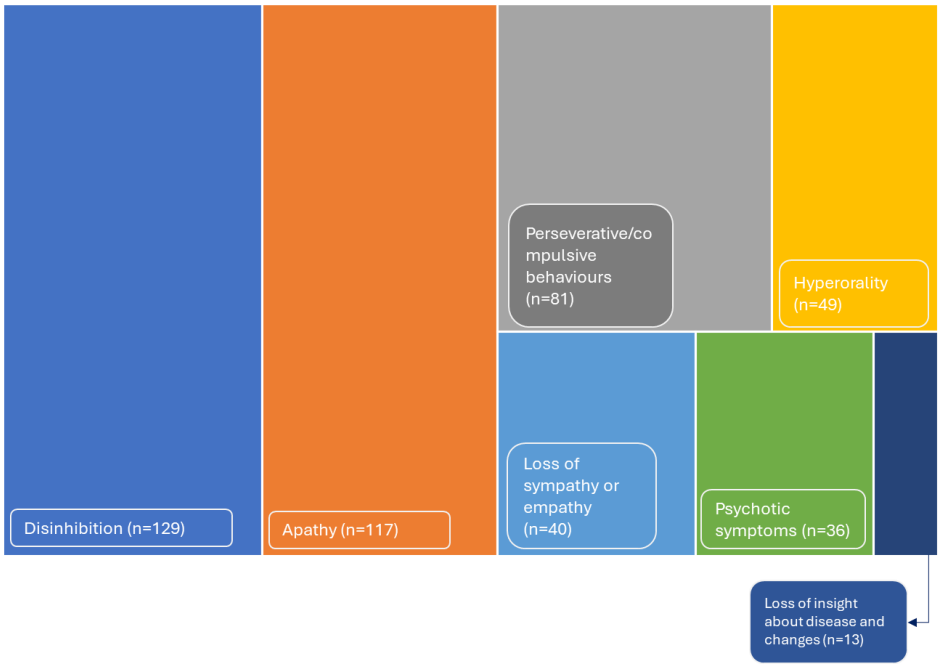

Figure 1

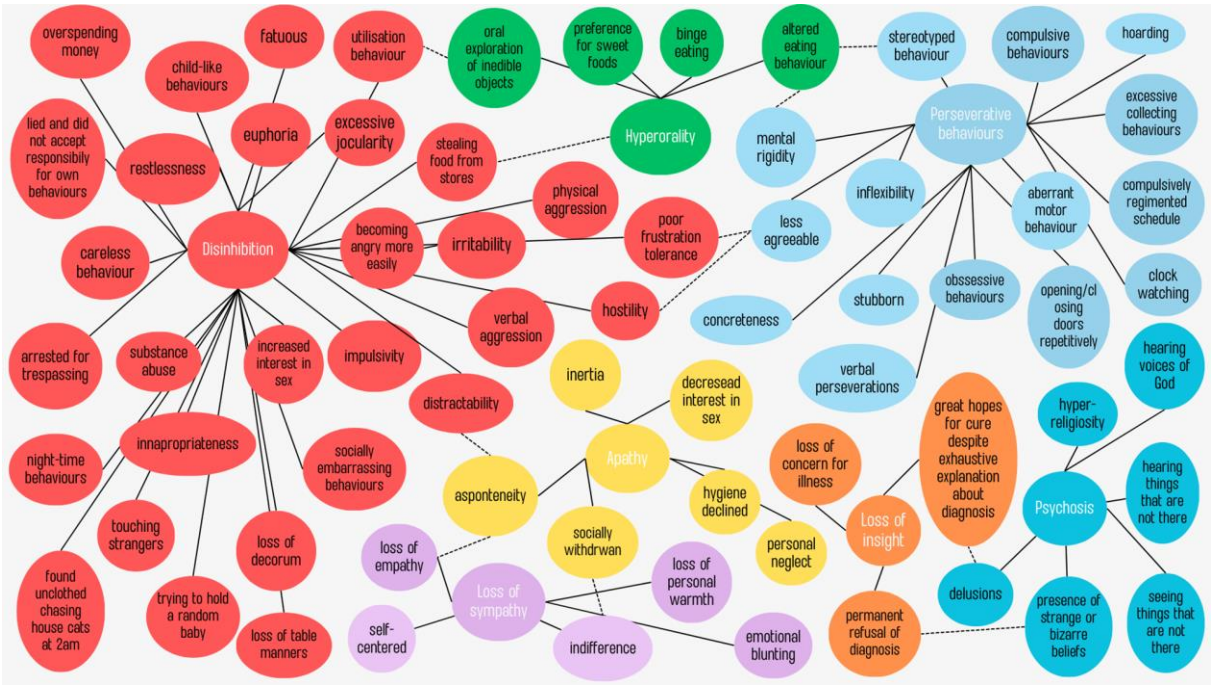

Figure 2