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Assessing the Stability of Clusters of Neuropsychiatric Symptoms in Alzheimer's Disease and Mild Cognitive Impairment

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ABSTRACT

Aim: The aim of the study was to investigate the factors that underpin neuropsychiatric symptoms and how they might evolve over time, in people with Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) dementia.

Background: Neuropsychiatric symptoms are psychiatric and behavioural manifestations that occur in people with AD. These are highly prevalent along the continuum of the disease, including at the stage of MCI, as well as before cognitive decline. Various small- and large-scale projects have investigated the underlying factors that underpin these symptoms, however, the identification of clear clusters is still a matter of debate; furthermore, no study has investigated how the clusters might change across the development of AD pathology, by comparing different time points.

Objective: Our objective was to investigate the factors that underpin neuropsychiatric symptoms in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), and to assess how the loadings might differ based on considerations such as disease stage of the samples.

Methods: Data was obtained from the Alzheimer's Disease Neuroimaging Initiative database (adni.loni.usc.edu), using scores from the Neuropsychiatric Inventory, followed up yearly from baseline until month 72. Participant groups included those with MCI or AD dementia, or a mixture of both, with all participants presenting with at least one neuropsychiatric symptom. A series of exploratory Principal Component and Factor (Principal Axis) Analyses were performed using Direct Oblimin rotation.

Results: The best-fitting structure was interpreted for each time point. A consistent unique structure could not be identified, as the factors were unstable over time, both within the MCI and AD groups. However, some symptoms showed a tendency to load on the same factors across most measurements (i.e., agitation with irritability, depression with anxiety, elation with disinhibition, delusions with hallucinations).

Conclusion: Although the analyses revealed some degree of co-occurrence of neuropsychiatric symptoms across time points/samples, there was also considerable variation. In the AD group, more discrete syndromes were evident at the early time points, whereas a more complex picture of co-occurring symptoms, with differences likely reflecting disease staging, was seen at later time points. As a clear and distinctive factor structure was not consistently identified across time points/samples, this highlights the potential importance of sample selection (e.g., disease stage and/or heterogeneity) when studying, for example, the neurobiological underpinnings of neuropsychiatric symptoms.

Assessing the stability of clusters of neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment

Keywords: Alzheimer's disease, mild cognitive impairment, neuropsychiatric symptoms, neuropsychiatric syndromes, behavioural symptoms, neuropsychiatric inventory, principal component analysis, factor analysis

1. Introduction

Neuropsychiatric symptoms are psychiatric and behavioural manifestations that occur in people with Alzheimer's disease (AD) and other dementias. These are highly prevalent along the disease continuum, with an estimated cumulative prevalence of 97% [1]. They can occur at the stage of Mild Cognitive Impairment (MCI), as well as before cognitive decline [2], which has led to the proposition of the label 'Mild Behavioural Impairment' to characterise people with these symptoms who are in a prodromal stage of the disease [3]. Although their classification varies across studies and according to the assessment tool employed, neuropsychiatric symptoms are typically identified as delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, aberrant motor behaviour, sleep disorders, and appetite/eating disorders [4]. They are associated with serious disabling effects, such as poorer cognitive and functional outcomes, earlier institutionalisation, accelerated disease advancement, caregiver distress, higher rate of progression from MCI to dementia, and increased mortality [5-7].

For these reasons, they are considered an important target for investigations to identify their underlying mechanisms and find effective treatment strategies [8]. Efforts have been made to identify sub-syndromes and more widely applicable theoretical models to explain the presence of neuropsychiatric symptomology. Furthermore, considering the complex symptomatology of dementia, having a sound theoretical base of how neuropsychiatric manifestations tend to co-occur has important implications for clinicians, in terms of a more accurate approach to management options and increased understanding of their etiopathology [9].

Neuropsychiatric symptoms often occur as a heterogeneous array of manifestations, fluctuating in presentation both between and within individuals across the disease course [10], which has contributed to the challenge to investigate them. Clarifying the patterns of their co-occurrence to identify distinct neuropsychiatric syndromes may help advance their assessment and treatment, as well as offer further clarity on their underlying mechanisms from a neuroanatomical and cognitive perspective [8].

Although in the past few decades, various small and larger-scale projects have approached this issue, according to a recent systematic review and meta-analysis [9], the identification of stable clusters is still unclear, as depending on the choice of statistical and analytical approaches, the assessment tool employed, and features of the samples (such as: type(s) of dementia included; whether a particular disease stage is selected or stratification used; varying sample-sizes), a considerable degree of variability can be evident, both in terms of the number of clusters that appear to best group the symptoms and the occurrence of each symptom in a particular cluster.

Concerning the statistical approach, most studies have performed exploratory factor analyses or principal component analyses (PCA). While these methods appear similar, they are based on different premises: PCA aims to reduce variables into smaller numbers of components, and is therefore useful to interpret patterns of co-occurrence, however, it is not intended to identify latent constructs, which is what can be interpreted from factor analyses [11]. Factor analysis can be carried out with an exploratory purpose, or alternatively confirmatory factor analysis may be used, which in this field, has been guided by clinically derived constructs [12].

While the most commonly used assessment tool is the Neuropsychiatric Inventory (NPI) [4], in its ten-item [13], twelve-item [14-17], or shortened (NPI-Q) version [18, 19], the best-fitting factor structure is debatable. Importantly, few investigations specifically explore these clusters within people with MCI [18] or consider the established frequency of these symptoms within MCI and how their presence at the earliest stages relates to the progression of AD pathology [20]. Further clarity on how neuropsychiatric syndromes might manifest in MCI would be useful to clarify the underlying mechanisms. Lastly, in terms of stability over time, no studies have investigated how the clusters might change within participants with AD over several years, which would reflect advancing disease severity and the progression of neuropathology.

Given these considerations, our aim is to investigate how neuropsychiatric symptoms may cluster over time (and might be impacted by issues such as disease progression). For this, we will carry out a series of exploratory principal component and factor (principal axis) analyses in samples of MCI and AD dementia participants [both separately and when pooled], using data made available from the large international database ADNI [21].

2. Materials and methods

2.1. Alzheimer's Disease Neuroimaging Initiative (ADNI)

The data was obtained from ADNI [21], a public-private partnership first launched in 2004, with the overarching goal of detecting AD at the earliest possible stages, tracking the disease's progression with biomarkers, and supporting advances in AD intervention, prevention, and treatment through the application of new diagnostic methods. The wealth of data in the ADNI database enables investigation of the relationships among the diagnostic features of AD and MCI at different time points, hence its suitability to address the objectives of this study. This importantly includes annual administration of the Neuropsychiatric Inventory, to allow a regular assessment of neuropsychiatric symptoms [4].

The present study used data from ADNI 2 [22] and 3 [23] protocols, specifically the Neuropsychiatric Inventory, in addition to the Mini Mental State Examination (MMSE) [24], and Clinical Dementia Rating Scale (CDR) [25].

Within the two aforementioned protocols, the studies were conducted according to Good Clinical Practice guidelines (details on the ethical considerations can be found at https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI-2_Protocol.pdf for protocol 2 and https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI3_Protocol.pdf for protocol 3). Written informed consent for the study was obtained from all participants and/or authorized representatives, who consented to all data being retained and stored within the database and used by researchers who have access.

2.2. Participants

The participants included in this study (Table 1) were people who had MCI or AD dementia, selected according to ADNI's inclusion criteria [22, 23]. Those in the AD dementia group presented with CDR of 0.5 or 1, and MMSE between 20 and 26. MCI participants had a CDR of 0.5 and MMSE between 24 and 30. MCI participants were excluded if they later developed other syndromes (e.g., dementia with Lewy Bodies, Parkinson's disease). While the MCI samples at early time points included participants that later converted to AD dementia and who are

therefore excluded from this group in analyses of later time points, the later time points, in addition to including people who later convert to AD dementia (or who have AD pathology and may still convert in the future), due to these exclusions, may potentially include an increased proportion of those with a non-AD aetiology. The selected participants had an assessment at baseline, and then annually until month 72. While some participants had data available beyond this, the sample sizes past month 72 were considered too small for our analyses. The samples were inclusive of participants that had scored positively on any of the neuropsychiatric symptoms at the time point selected for the analysis, thus participants were excluded if they did not present with any of the neuropsychiatric symptoms at that specific time point. While this procedure of participant selection maximised sample size at each time point, it meant that exactly the same set of participants may not, therefore, have featured at every time point.

Although recommendations for sample size requirements in factor analyses are not unequivocal [26], we primarily aimed for the criterion of 10:1 ratio of participants-to-variables [27], and therefore, groups that had more than one hundred and twenty participants. An exception was made for the AD group at 24 months, which, although having a ratio of 8.9:1, was deemed adequate by the Kaiser-Meyer-Olkin [28] and Bartlett's [29] test for factor analyses. For this reason, we could investigate the MCI samples for the first four time points (from baseline to month 36), the AD samples from baseline to month 24, and for the last three time points, we could only provide analyses based on the total (pooled) samples.

In addition to the main set of analyses described above, that were carried out on the samples selected for maximum size, a further set of analyses were performed on subsets of the sample (consisting of an AD group and an MCI group) that were tracked longitudinally, and in which the participant numbers remained constant across the available time points. These analyses consisted, once again, of principal component and factor analysis, carried out separately on each subgroup at each available time point (see Supplementary Tables S1-S6). From here on, for clarity, these alternative sets of analyses will be referred to as the "supplementary analyses". The time points selected were those that had large enough numbers of AD samples and MCI samples available, that were sufficient for the chosen analysis methods (for descriptives, see Table S1; for MMSE scores, see Figure S1). Participants were included if they scored positively on at least one symptom, on at least one of the selected time points. Those participants who dropped out had their data from the earlier time points removed. Due to the restrictions in sample sizes that were available due to this process, within the AD sample it was only possible to analyse baseline data and month 12, while for the MCI sample it was possible to analyse from baseline up to and including month 36. In the analysis focusing on MCI, participants who had MCI were selected at baseline, and both the participants remaining with MCI and those who then developed AD were included in the analyses at each time point (with the group composition reported in the Table S6). These additional supplementary analyses allowed the stability of the clusters to be tested within groups with the same sets of participants at each available time point, thus excluding the potential altering element of the substantial rate of dropout.

2.3. Assessment of neuropsychiatric symptoms

The Neuropsychiatric Inventory (NPI) [4] is a well-validated, reliable, multi-item instrument based on caregiver interview, aimed at evaluating twelve neuropsychiatric features: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviour, sleep disturbances and appetite

disorder. It is a retrospective, informant-based rating scale, within which the interviewer poses a screening question for each symptom to assess behaviours that have appeared or changed since the onset of illness.

The scoring system of the NPI allows coding of the presence of the symptom, as well as the frequency (on a scale of 1 to 4, 1 corresponds to Occasionally, 2 to Often, 3 to Frequently, 4 to Very frequently), severity (1 to 3, 1 corresponds to Mild, 2 to Moderate and 3 to Marked), and total score, which is the product of the two measures (1 to 12). Included in the analyses to determine the factor structure were scores of 0 (should the symptom be absent) and should the symptom be present, total scores ranging from 1 to 12 (which, due to the scoring options that are available for frequency and severity, and means of score calculation, excludes scoring options of 5, 7, 10 and 11).

2.4. Statistical analysis procedure

Principal component analyses (PCA) and factor analyses (using the principal axis extraction method) were performed on IBM SPSS, Version 28.0.1 [30]. PCA was employed first to explore the patterns of co-occurrence of symptoms, given that this method extracts the maximum variance from the data set for each component [31]. Then, we proceeded to perform principal axis analyses, in order to explore the underlying latent constructs. With respect to rotation, we explored the stability of the factors by comparing two oblique rotation methods, the Direct Oblimin (primarily), and Promax (to confirm the stability of the clustering); compared to the more common orthogonal Varimax, oblique rotation methods provide the advantage of considering correlations among the factors, as was expected in these datasets.

With respect to the interpretation procedure [11], first, we explored the structure derived by selecting Eigenvalues greater than one [32], considering the items that significantly loaded on a factor (cut-off value of 0.4) and the interpretation of the scree plots [33]. Subsequently, different fixed numbers of factors (two, three, four, or five) were selected, based on the interpretation of the scree plots, the total variance explained (minimum threshold set at 40% of the total variance explained by the model), independence of factors (avoiding symptoms loading on multiple factors, and lower correlations among factors), to determine the best-fitting model at each time point.

3. Results

3.1. Descriptive statistics

The main characteristics of the samples that were analysed and the main demographic aspects such as age, gender, and education, are depicted in Table 1.

The mean MMSE scores are depicted in Figure 1, which shows the variation over time, based on group: within AD these show a decreasing trend, ranging from 22.90 at baseline to 19.20 at the last time point, which indicates progression of the disease, while in MCI group these were recorded as slightly below 28 at all time points (i.e., they were not observed to decrease over time, probably due to the criteria applied for classification of MCI and that a person's classification would change, for example, should they decline and covert to dementia, leading to exclusion from this group).

3.2. Prevalence and progression of neuropsychiatric symptoms

The prevalence of neuropsychiatric symptoms (percentage of people exhibiting each symptom) according to the three samples (MCI, AD, and combined total samples) at each time point is depicted in Table 2. Tables 3 and 4 depict the averages of the total NPI scores (frequency multiplied by severity) across each group (MCI, AD, and combined total samples), and illustrate how the symptoms differed in their presentation at each time point. Table 3 is only inclusive of participants who presented with a score of 1 or higher (in other words, those who presented with the reported symptom), while Table 4 is also inclusive of participants who presented with a score of 0, so this calculation includes also those people also who did not have the reported symptom (and therefore reflects the impact of symptom presence, frequency and severity together).

Considering first, the prevalence of each symptom within each of the samples, Table 2 shows, overall, a slightly lower occurrence of symptoms in MCI compared to AD, with the exception of sleep disturbances which consistently occurred more in MCI; furthermore, while in AD prevalence tended to increase from baseline to the following measurements, the values recorded for MCI appeared more stable.

Within the groups of participants with a diagnosis of AD, the most prevalent symptoms were apathy (45.0 - 56.9%), depression (37.7 - 54.1%) and irritability (35.8 - 48.4%), and the least prevalent symptoms were elation (ranging from 1.6 - 11.3%), hallucinations (6.7 - 18%), and delusions (10.6 - 18.1%). In terms of the neuropsychiatric symptom total scores (frequency multiplied by severity), Table 3 and 4 show that the average total NPI scores were typically higher in AD compared to MCI. When calculated using the scores of those who presented with each symptom of interest only (Table 3), fluctuations can be noted across time points, with no symptom increasing across every time point. By including in the averages also those who scored zero (who did not have the symptoms), hallucinations, depression and aberrant motor behaviour all had their highest scores at month 72 (Table 4).

For the MCI groups, a somewhat similar trend was observed in terms of the overall pattern of all symptoms, with slightly lower prevalences overall compared to AD: the most prevalent symptoms were irritability (ranging from 37.7 – 51.7%), depression (37.0 – 47.5%) and sleep disorder (28.3 – 40.9%), while the least prevalent symptoms, like the AD group, were hallucinations (ranging from 0 to 2.3%), delusions (0.7 - 5%), and elation (0 - 4.6%). The average total NPI scores for each symptom, as calculated using only the scores of those who had the symptoms (Table 3), again showed considerable fluctuation across time points, with sleep, agitation and depression having their highest scores at month 72, while apathy, disinhibition, irritability, appetite disorder, and anxiety were highest at month 60. Considering the averages of all scores, including those of zero (who did not have the symptom), differences in the time points where the highest scores were observed in Table 3, were in irritability, which was highest at month 72, sleep, at month 48, and apathy, at month 36 (Table 4).

For the supplementary analyses, that were carried out on the participant samples that were tracked over time, and for which each time point contained the same number of participants, for the AD group, the symptoms of greatest prevalence (see Table S2) were apathy (ranging 44.8 - 48.9%), agitation (30.6 - 31.3%), depression (38.7 - 39.4%) and irritability (34.0 - 37.4%). Those with the lowest prevalence were elation (ranging 3.4 - 4.7%) and hallucinations (6.2 - 7.4%), while the greatest increases over time were observed in delusions (8.9 increasing to

17.0%) and aberrant motor behaviour (16.3 increasing to 25.8%). The average score (frequency X severity), irrespective of whether only people with the symptoms were included in the calculations or not (see Table S3 and S4), increased across time points (baseline to month 12) for every symptom.

For the supplementary analyses on the group who were classified as MCI at baseline, and followed over time, the symptoms of greatest prevalence (Table S2) were, depression (ranging 31.0 - 33.1%), anxiety (15.2 increasing to 21.5%), irritability (25.2 increasing to 32.1%) and sleep disorder (26.3 – 28.9%); the lowest prevalence were hallucinations (1.0 increasing to 6.3%), delusions (2.1 increasing to 4.2%), and aberrant motor behaviour (2.6 increasing to 10.0%), and the greatest increase was in apathy (17.8 increasing to 29.4%). The average scores (see Tables S3 and S4) fluctuated more in the MCI group, and only apathy increased across all time points (baseline to month 36) irrespective of whether only people with the symptoms were included in the calculations or not.

3.3. Preliminary assumption testing

Prior to proceeding with the factor analyses, assumptions were tested using SPSS, Version 28.0.1 [30]:

- Correlation among variables (correlation matrix) did not show loadings >.80;
- Kaiser-Meyer-Olkin [28] and Bartlett's [29] test for factor analyses showed the adequacy of the sample sizes.

3.4. Interpretation of the component/factor structures

Exploratory principal component and principal axis factor analyses were performed on the three groups (total sample, AD, and MCI), at each time point available.

The factors/components reported in tables 5, 6, and 7 reflect the best-fitting models for the total sample, AD group, and MCI group, respectively. These were interpreted by comparing the different rotation methods, based on the following considerations:

- Eigenvalues greater than 1;
- Item loadings on the factors were greater than 0.4;
- Interpretation of the scree plot patterns (available in supplementary materials);
- Minimum 40% total variance explained by the model;
- Best achievable independence of factors (based on the following criteria: lower correlation among factors, few/no cross-loading of items on more than one factor).

3.5. Results of the main analyses on the samples selected for maximum size

The results of the total sample group (inclusive of AD and MCI participants) are reported in Table 5. At baseline and month 12, the best-fitting structure according to the above criteria was with four components/factors, which accounted for more than 50% of the total variance. The symptoms loading on a component/factor were not completely consistent over the two methods, and at the two different time points, however, some pairings of

symptoms emerged as: symptoms related to affect/mood (depression and anxiety); symptoms related to hyperactivity (agitation and irritability); symptoms related to impulse control and hypomania (disinhibition and elation); psychotic symptoms (delusions and hallucinations). Other symptoms related to apathy, aberrant motor behaviour, as well as neurovegetative functions (sleep disorders and appetite disturbances) tended to vary more frequently in terms of the components/factors onto which they loaded. From month 36 to 60, a three component/factor structure best described the data, explaining more than 40% of the variance, while for month 72, more than 40% of the variance and best-fitting model was obtained by two components/factors. Across these time points, the associations described above were found to a certain degree, but still with considerable variance (visually depicted in Figure 2).

The results of the analyses performed considering only participants with AD dementia are reported in Table 6. Here, five components/factors were found to better explain the model at baseline, evidencing similar dimensions as found in the total sample analyses, which can be described as affect/mood, impulse control/hypomania, psychosis (with sleep disturbances), hyperactivity, and lastly apathy with appetite disturbances. In the two subsequent time points analysed, on the other hand, a three component/factor structure fitted better, explaining 48% (month 12) and 54% (month 24) of the variance. At both time points, the first component/factor was composed of psychotic (delusions and/or hallucinations), affective (depression and anxiety), and hyperactive elements (agitation and irritability), while the other two were mainly: apathy with aberrant motor behaviour, and impulse control/hypomania-related symptoms (disinhibition and elation).

Lastly, concerning Mild Cognitive Impairment (Table 7), the best-fitting structure varied from four at baseline (with 47% of variance), three at months 12 and 36 (respectively, explaining 41% and 49% of variance), and five at month 24 (59%). Here, only the pairing constituted by agitation and irritability found in AD and in the total samples was confirmed, while the other symptoms tended to load on differing components/factors: there was an overlap of psychotic and affective components (i.e., depression with delusions and/or apathy, hallucinations with anxiety), and overlap of elation and/or disinhibition and aberrant motor behaviour to the hyperactivity elements.

Figures 3 and 4 illustrate the factors derived from the AD and MCI subgroups, respectively, showing the frequency of co-occurring clusters of symptoms over time.

3.6. Results of supplementary analyses on the tracked participants

The same interpretation methods and criteria described above for the main analyses (in which sample size was optimised for each time point) were applied to this set of analyses (where the same set of participants were present for all time points). Tables S5 and S6 reflect the best-fitting models of the principal component and factor analyses for the AD group and MCI group, respectively.

Similar results were found when analysing these samples as were found for the main analyses. Specifically, the components/factors were again seen not to be entirely consistent over time. However, some pairings did emerge, which corresponded with those identified in the main analyses. The main difference found was in the number of component/factors identified (see below), which may be due to the differences in sample sizes between the two analyses (with the supplementary ones having smaller samples overall).

Only baseline and month 12 could be analysed for the AD sample, which consisted of 147 participants (Table S5). A four component/factor structure best fitted the data, and the most consistent pairings were agitation with irritability, depression with anxiety, elation with disinhibition, and sleep with appetite, while the overall composition of the components/factors and the clustering of other symptoms varied substantially.

Lastly, concerning the MCI at baseline sample (with subsequent time points including participants who remained at MCI and those who developed AD), were analysed up to month 36 (Table S6). In this case, the first three time points were better described by a four component/factor structure, while at month 36, five components/factors better fitted the data. Similarly to the main analyses, the components/factors were not consistent over time. Agitation with irritability remained the only pairing identified in the AD group, which was consistently found in this group as well. Sleep with appetite, and elation with disinhibition were identified at most time points, and new pairings emerged which were not identified in the AD group, of hallucinations with anxiety, and depression with delusions, apathy, and/or appetite.

4. Discussion

To our knowledge, this is the first study which investigates the factors of neuropsychiatric symptoms over several time points and within distinct samples of Alzheimer's disease and Mild Cognitive Impairment. The results indicate that a single unique structure cannot be identified, as the factors derived were not consistently stable, suggesting that there is variability over time (introduced, for example, through sample heterogeneity and the disease stage of the participants). It should be noted, however, that a selection of symptoms did load together for most time point measurements: some consistently across both the AD and MCI groups, while others only within one of the two groups, indicating a tendency of those symptoms to co-occur.

Comparable conclusions can be drawn from the supplementary analyses, carried out on the subset of participants who had measurements available at all the time points selected (results tables can be found in the supplementary material). In those analyses, by reducing the heterogeneity of the samples, through excluding participants who dropped out of the study at subsequent time points (for reasons unknown and not recorded in the dataset), similar to the main analyses, a single unique structure could again not be identified. Across the analyses, comparable pairings of symptoms tended to be seen over time, some consistently across AD and MCI groups, and others specifically for one of the two groups, while other symptoms showed substantial variation over time (in all participant groups).

Starting by considering the number of factors/components that represented the best-fitting model, compared with previous studies, this was only partially consistent: while a four-factor structure has been most commonly proposed [14, 15], in the latest time points of the AD and total sample subgroups our data was better interpretable (i.e., presenting less cross-loading symptoms over multiple factors, and/or factors explained by only one variable) with fewer factors, such as three or two. This might relate to the more limited sample-size available for those analyses (see limitations section below), compared to the earlier time points, however, this tendency of identifying fewer factors over time was not reflected within the MCI subgroup analyses, for which the sample sizes also decreased. Therefore, it might be more likely to indicate a tendency of neuropsychiatric symptoms to be more intercorrelated and less clear over time. This pattern might relate to the progression of neurofibrillary tangle

neuropathology [34-36]. While at earlier stages of disease the symptoms manifested are more heterogeneous, which might explain why clearer syndromes were identifiable at the initial measurements, studies that have investigated the correlation between neuropsychiatric symptoms and advanced neuropathological changes [35] have identified the presence of several overlapping symptomatologic dimensions (more than eight symptoms experienced by each individual). Our results seem to be consistent with this notion: as the pathology advances, neuropsychiatric syndromes that appear to be distinguishable at earlier stages of the disease tend to overlap in their presentation.

4.1. Symptoms relating to hyperactivity

Agitation and irritability, two of the most prevalent symptoms in our samples of both MCI and AD participants, were one of the most consistently paired symptoms over time and when considering the groups of MCI and AD participants together and separately. These symptoms were also found to load on the first component/factor (therefore were responsible for the majority of the variance explained) quite consistently across measurements. This was also the cluster which was most consistently confirmed by the supplementary analyses of both AD and MCI samples, and it was identified in both groups at all time points. Identification of this factor is also in line with the majority of the literature [9], which has proposed a 'hyperactivity' component, that is also evident during the MCI stage [18]. The stability of this clustering over time has been previously proposed by a study on an AD sample that performed factor analyses every six months over a two-year period of time [37]. The clustering of these symptoms is typically reported as independent [15, 17, 38], but can include other symptoms such as aberrant motor behaviour [14]. In our samples we found them to cluster together quite often with depression and anxiety, particularly in AD [39, 40], and with aberrant motor behaviour, disinhibition, and elation more frequently in MCI.

4.2. Symptoms relating to impulse control and hypomania

Disinhibition and elation were frequently identified together as a unique cluster in the AD group, which could be termed a 'impulse control' or 'hypomanic' component, previously identified in other studies [40]. In MCI, however, they did not load together, but instead, at various time points, in particular for disinhibition, there was overlap with the hyperactivity symptoms mentioned above, similar to what was previously found [16] (agitation, irritability and disinhibition) and [41] (agitation, irritability and elation). Both symptoms were also found to load with aberrant motor behaviour. Similar results were found in the supplementary analysis of the AD group, while in the MCI group, these symptoms still tended to load together at most time points, albeit frequently in the same factor as aberrant motor behaviour.

4.3. Symptoms relating to affect and mood

The 'affective' symptoms of anxiety and depression were found to load together mostly within the AD group. Other than presenting with high comorbidity in psychiatric conditions [42] underlined by key neurobiological mechanisms, for example, linked to synaptic disruption [43], an association between these two symptoms is supported by previous factor analyses in AD [14, 37, 44], and was generally confirmed in our study. In terms of their associations with other symptoms, over several time points they clustered with hyperactivity-related symptoms, and on some occasions with one or both psychotic symptoms (delusions and hallucinations). In MCI,

however, they only clustered together at baseline; interestingly, both symptoms were found to cluster with psychotic symptoms in the MCI group, but with different patterns: anxiety with hallucinations, and both affective symptoms, but mostly depression, with delusions. Similar patterns were also observed in the supplementary analyses: while in AD, they clustered together at both time points, in MCI they were associated with psychotic symptoms in the same manner as in the main set of analyses. Associations between affective symptoms and psychotic symptoms in psychiatric conditions are well established in the literature [45]; furthermore, previous studies on AD populations have proposed an association between depressive symptoms and psychotic symptoms, moderated by genetic factors [46, 47] and between depression and delusions specifically [48, 49]. However, previous factor analyses on neuropsychiatric symptoms within AD and MCI have not typically reported this distinct clustering, and particularly the association between hallucinations and anxiety within the context of MCI has not been investigated in depth so far. Lastly, depression was also found to load with apathy, mostly in MCI and in the total sample; this pairing was previously proposed by a study which investigated a sample inclusive of MCI and AD dementia participants [13], as well as studies which focused on AD participants only [12, 15]. Further clarity on the relationship between depression and apathy is currently a matter of investigation [50]: the two symptoms share commonalities in their clinical presentation, to the point of having partially overlapping diagnostic criteria [51], which has made them hard to distinguish within the context of AD. However, recent studies [52, 53] suggest that particularly in AD, they ought to be considered as two distinct syndromes, based on aspects such as: their neurobiological origins, behavioural features, and associations with other neuropsychiatric symptoms (for example, depression but not apathy tends to associate with anxiety, while apathy but not depression with aberrant motor behaviour). A further argument for the distinction between the two symptoms has also been made when considering the association of apathy and depression with anosognosia (which describes when someone is unaware of their disorder or when they underestimate its affects) within the context of AD: while apathy appears to increase with anosognosia, depression correlates with lower anosognosia (therefore higher awareness) [54].

4.4. Psychotic symptoms

A 'psychotic' cluster (delusions and hallucinations) within AD has been previously suggested, based on genetic findings [55] and previous factor analyses, which quite consistently identified them typically as a stand-alone factor/component [13, 15, 17], and at times inclusive of other symptoms, for example, sleep disturbances [14] or disinhibition [38, 41]. This was confirmed in our analyses to a degree: while within the AD group and the total sample group, we did find delusions and hallucinations to frequently cluster together, there was some fluctuation in the stability of their co-occurrence over time, which seems to suggest a degree of difference in terms of underlying mechanisms between the two symptoms, particularly with the progression of AD pathology, as proposed, for example, by neuroanatomical studies [56]. Psychotic symptoms were also found to frequently cluster together with symptoms relating to affect, hyperactivity, hypomania, sleep disturbances, and aberrant motor behaviour, and particularly at the latest time points, where presumably AD pathology was greater, they tended to form part of larger clusters inclusive of different symptomatologic dimensions (for example, factors/clusters inclusive of hyperactive, affective, and psychotic elements). Lastly, as mentioned above, co-

occurrence with depression and anxiety were particularly relevant within MCI, and the nature of these associations at this stage of the disease would be interesting to explore further.

4.5. Apathy

While it did co-occur with several other symptoms, a clear and stable relationship to other symptoms could not be identified in our analysis for the symptom of apathy. This seems to be in line with previous factor analyses, which tend to find apathy to either load over multiple factors, or to constitute a stand-alone factor [9]. Despite this being the case in our analysis at some time points, some correspondence could be identified between apathy and appetite disturbance, which has been previously suggested [14, 17, 37, 57] and might relate to the lack of motivation to eat [53]. Apathy was also found to be associated with depression, as mentioned above, particularly in MCI, and with aberrant motor behaviour, in a 'psychomotor' component [41]. Considering that apathy is one of the most prevalent and clinically relevant symptoms, further investigations to clarify its origins and co-occurrence with other neuropsychiatric symptoms would be useful.

4.6. Aberrant motor behaviour

Similarly to apathy, aberrant motor behaviour did not co-occur with other symptoms frequently enough to be identified within a single component/factor. Consistent with the literature, however, the most frequent associations were either with apathy [40, 41], or with symptoms relating to hyperactivity and disinhibition [12, 16, 37, 44].

4.7. Sleep disturbances and appetite disorder

A co-occurrence of 'neurovegetative' symptoms (sleep disturbances and appetite disorder) was identified within the MCI samples. As there are not many factor analyses available that focus on MCI only, and this cluster has not been previously suggested, it might be interesting to investigate further, considering their established interrelated associations, explained by hormonal models underpinning the mechanisms of these two functions [58]. Within AD and the total samples, on the other hand, these two symptoms were found to fluctuate on different factors, which is not uncommon across the literature [59]. As mentioned, appetite disorders were most frequently linked with apathy. Sleep disturbances instead co-occurred with psychosis at some time points, within AD and the total sample. Slightly different results were found in the supplementary analyses: while in MCI they were still found to load together, in this case they were also found in the same cluster within the AD group, while co-occurring with apathy. While studies on psychiatric conditions, such as schizophrenia, as well as non-clinical populations [60] have suggested an association between different aspects of sleep disturbances and delusions and hallucinations, only some previous factor analyses on AD samples found this association of sleep with psychotic symptoms [14]; one longitudinal investigation on AD samples [37] found them to fluctuate over time, as we typically found, suggesting that further exploration of this association might be interesting. Lastly, it is interesting to note that sleep disturbances were the only symptoms that presented with a higher frequency in MCI compared to AD, a finding replicated in the supplementary analysis as well; considering the impact that sleep may have during the earliest stages of the disease, more research is needed to understand the role this plays in the progression of AD pathology [34, 61].

4.8. Limitations

Some limitations should be noted: first, in terms of sample sizes, although all but one of our analyses complied with the minimum sample-size for factor analyses according to frequently applied criteria [26, 27], and that one did, however, fulfil the other requirements considered for the adequacy of sample size [28, 29], it would be useful to repeat the analyses on larger datasets, with a ratio of at least 20:1 observations per variable, in order to minimise error [26]. Concerning the MCI samples, although we excluded those who developed other syndromes, we included both individuals who had MCI at earlier time points and then progressed to AD dementia and those who remained with an MCI classification at later time points, which given the uncertainty of disease aetiology, might be a confounding factor in terms of symptom co-occurrence and clustering. Due to the limitations of sample size and characteristics, we did not perform further stratification to account for aspects such as gender, age, education, ethnicity, or genetic profile, which would be an interesting future direction.

5. Conclusion

In conclusion, although some degree of consistency existed for certain symptom clusters, we did not identify a single factor structure across the time points and that fitted both people with AD and MCI, neither in the main set of analyses, nor in the supplementary analyses. Within AD, it was possible to identify clearer syndromes at earlier stages, while at the latest time points, the symptoms tended to overlap in more complex clinical pictures (for example, constituted of hyperactivity, affect and psychotic symptoms). Considered the paucity of investigations in MCI, it would be useful to perform further investigations to explore, for example, the clusters found in this study, which were not previously suggested, such as hallucinations and anxiety, or sleep disturbances and appetite disorder. Considering the future, our study suggests that on the one hand, the more consistent instances of co-occurrence of symptoms found within AD and MCI should be taken into account in studies that attempt, for example, to understand the mechanisms underpinning symptoms (e.g., by considering what features are shared or unique for each symptom). On the other hand, the differences across the time points and between AD, MCI, and the total sample, illustrate the importance of considering aspects such as disease stage and heterogeneity of the sample during study design (and recruitment) and/or during the statistical analyses.

Conflict of interest

None.

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Figure 1. MMSE scores on the total sample, MCI, and AD samples.

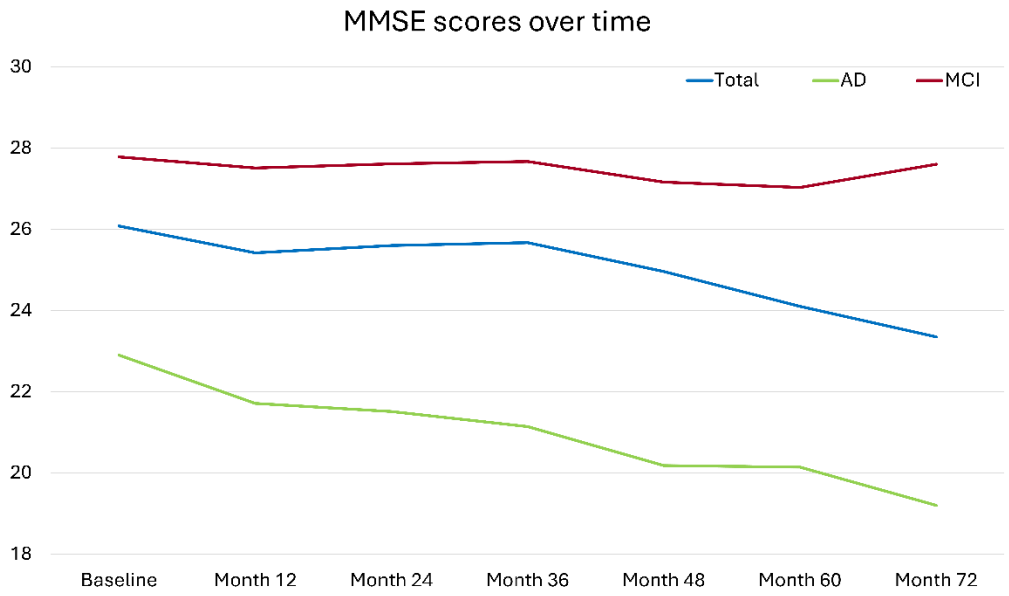
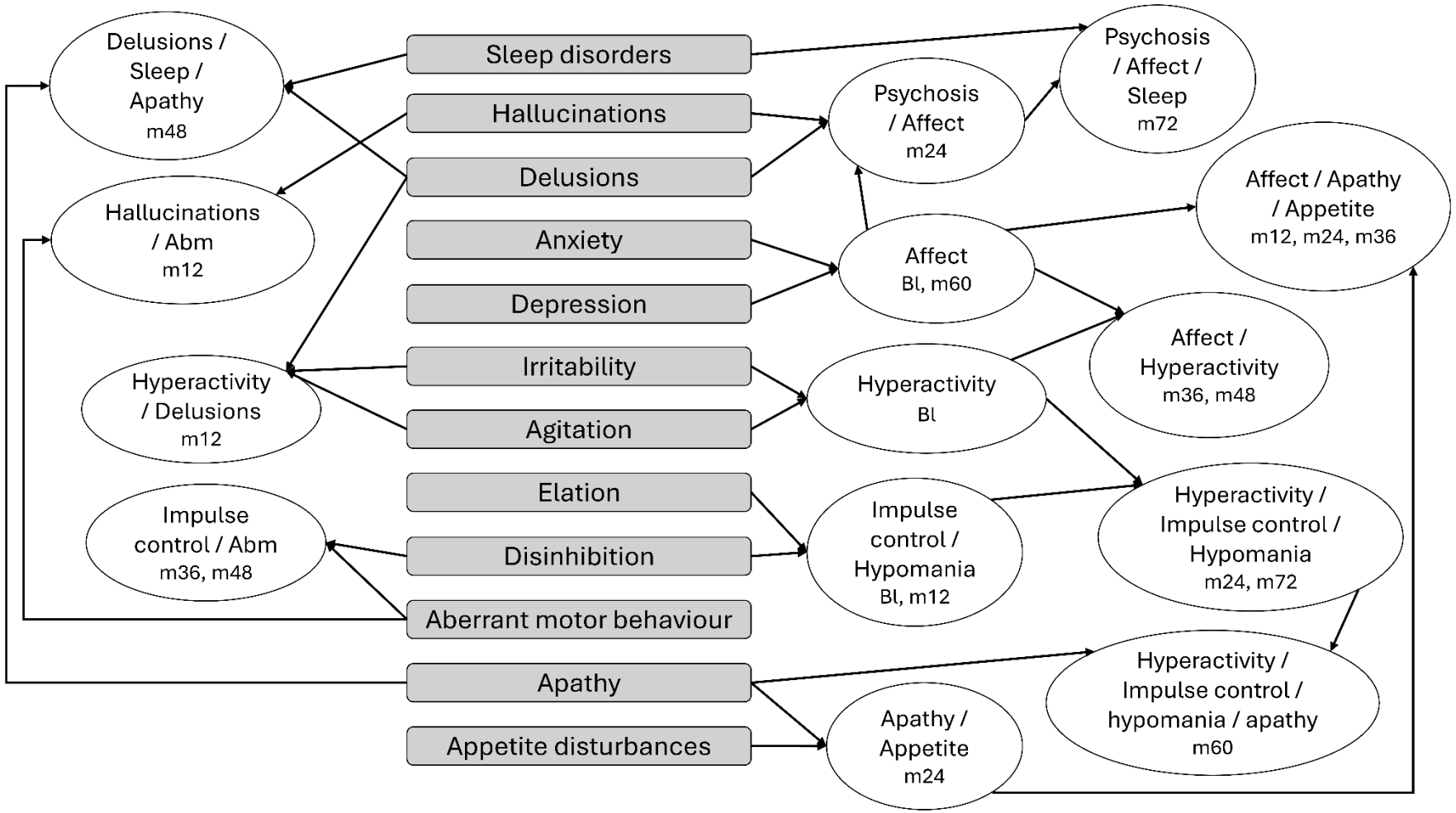


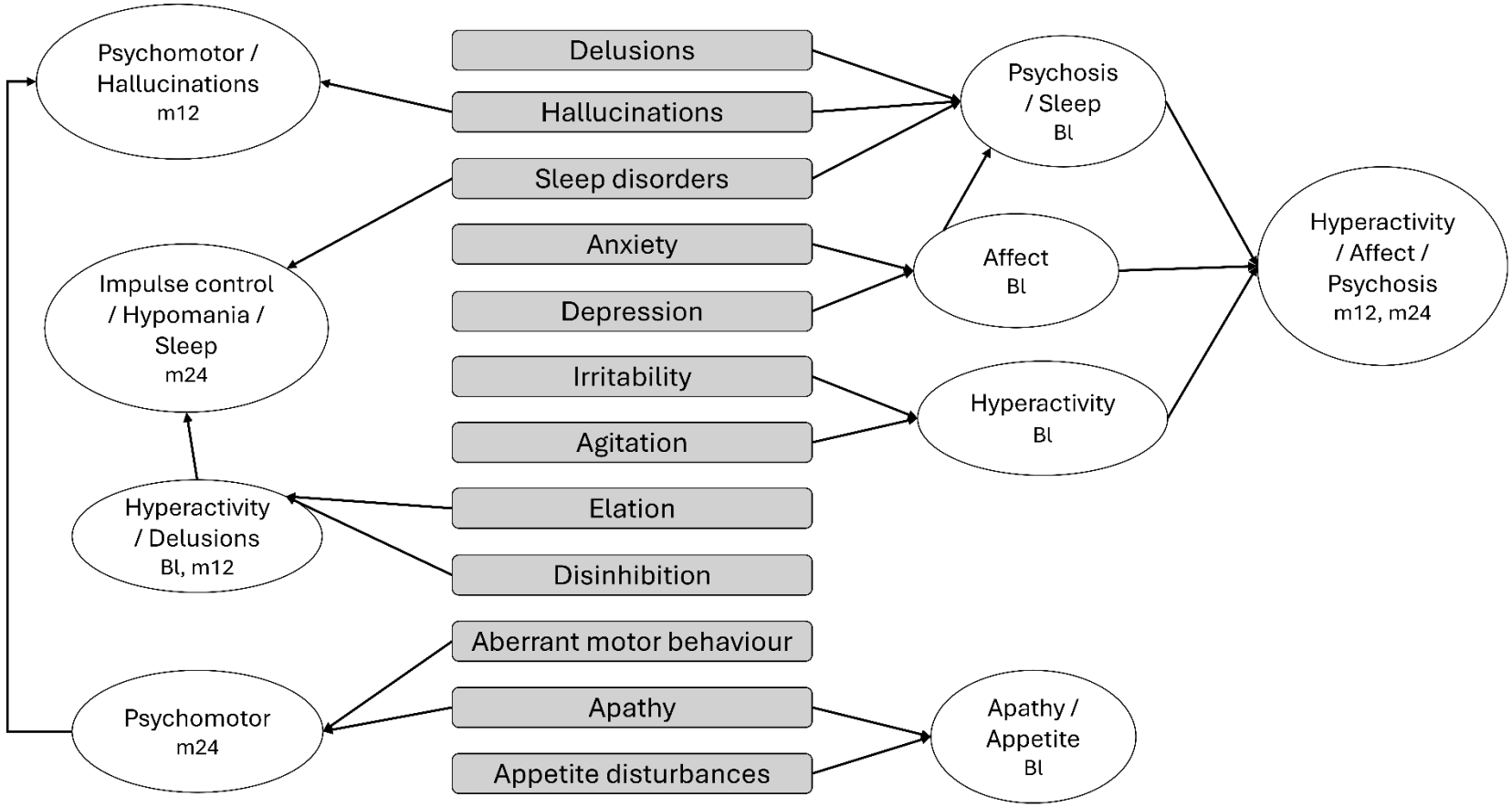
Figure 2. Overview of the factors resulting from the Principal Axis Factor Analysis in the total samples.



Notes. The figure shows the neuropsychiatric symptoms (rectangles) and the factors they were found to load on to (ovals) at the different time points. This illustrates how at baseline, the factors reflect more defined neuropsychiatric syndromes, while with the progression of AD pathology these tend to become more complex (i.e., composed by multiple syndromes).

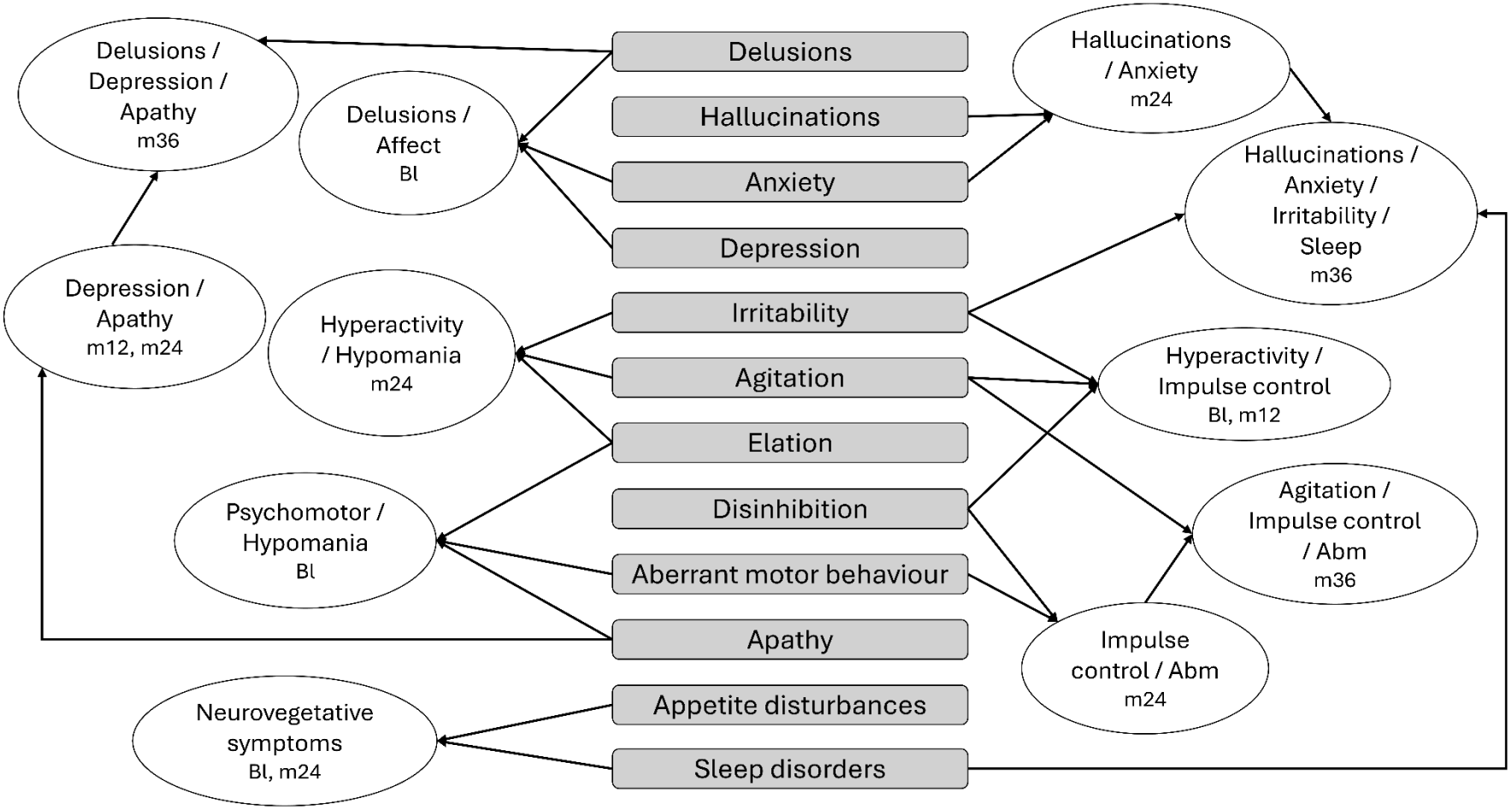
Abbreviations: bl=baseline; m=month

Figure 3. Overview of the factors resulting from the Principal Axis Factor Analysis in the AD sub-group.



Notes. The figure shows the neuropsychiatric symptoms (rectangles) and the factors they were found to load on to (ovals) at the different time points. This illustrates how at baseline, the factors reflect more defined neuropsychiatric syndromes, while with the progression of AD pathology these tend to become more complex (i.e., composed by multiple syndromes).
Abbreviations: bl=baseline; m=month

Figure 4. Overview of the factors resulting from the Principal Axis Factor Analysis in the MCI sub-group.



Notes. The figure shows the neuropsychiatric symptoms (rectangles) and the factors they were found to load on to (ovals) at the different time points. This illustrates how within MCI, more variation was found between neuropsychiatric syndromes at the different time points, and a pattern could not be identified to explain the difference between earlier and later time points.
Abbreviations: bl=baseline; m=month; abm=aberrant motor behaviour.

Table 1. Participant information.

Time point	Sample Size	Age	Gender	Education	MMSE
Baseline	517 total	μ=72.19	F=211	μ=16.02	μ=26.08
		SD=9.56	M=306	SD=2.63	SD=3.13
	180 AD	μ=74.81	F=72	μ=15.64	μ=22.90
		SD=7.86	M=108	SD=2.62	SD=2.31
	337 MCI	μ=70.79	F=139	μ=16.24	μ=27.78
		SD=10.08	M=198	SD=2.61	SD=1.96
Month 12	443 total	μ=73.67	F=191	μ=15.95	μ=25.42
		SD=8.28	M=252	SD=2.67	SD=4.30
	160 AD	μ=74.88	F=69	μ=15.75	μ=21.71
		SD=7.68	M=91	SD=2.62	SD=4.68
	283 MCI	μ=72.98	F=121	μ=16.07	μ=27.51
		SD=8.53	M=162	SD=2.70	SD=2.11
Month 24	324 total	μ=74.01	F=133	μ=16.01	μ=25.60
		SD=7.7	M=191	SD=2.61	SD=4.95
	107 AD	μ=74.98	F=42	μ=15.85	μ=21.51
		SD=8.25	M=65	SD=2.7	SD=5.14
	217 MCI	μ=73.54	F=91	μ=16.09	μ=27.61
		SD=7.36	M=126	SD=2.56	SD=2.21
Month 36	200 total	μ=74.78	F=83	μ=16.05	μ=25.67
		SD=7.06	M=117	SD=7.06	SD=4.76
	62 AD*	μ=75.64	F=29	μ=16.17	μ=21.14
		SD=6.75	M=33	SD=2.42	SD=5.90
	138 MCI	μ=74.40	F=54	μ=15.99	μ=27.67
		SD=7.17	M=84	SD=2.58	SD=2.04
Month 48	168 total	μ=76.09	F=73	μ=15.84	μ=24.96
		SD=6.79	M=95	SD=2.54	SD=4.91
	53 AD*	μ=75.26	F=26	μ=15.62	μ=20.18
		SD=6.35	M=27	SD=2.55	SD=5.57
	115 MCI*	μ=76.45	F=47	μ=15.94	μ=27.16
		SD=6.96	M=68	SD=2.53	SD=2.35
Month 60	137 total	μ=78.23	F=46	μ=15.77	μ=24.10
		SD=7.04	M=91	SD=2.94	SD=5.15
	60 AD*	μ=78.41	F=20	μ=15.66	μ=20.14
		SD=6.57	M=40	SD=2.73	SD=5.29
	77 MCI*	μ=78.09	F=26	μ=15.85	μ=27.03
		SD=7.39	M=51	SD=3.09	SD=2.29
Month 72	121 total	μ=79.65	F=50	μ=15.65	μ=23.35
		SD=7.21	M=71	SD=2.87	SD=6.11
	61 AD*	μ=80.26	F=30	μ=15.78	μ=19.20
		SD=6.90	M=31	SD=2.70	SD=5.80
	60 MCI*	μ=79.03	F=20	μ=15.51	μ=27.60
		SD=7.46	M=40	SD=3.03	SD=2

Notes. *At these time points, analyses on AD and/or MCI sub-groups were not performed, due to sample size lower than 10:1 ratio. Exception was made for m24 AD group, that had an 8.9:1 ratio, as it was deemed adequate by the Kaiser-Meyer-Olkin (Kaiser, 1974) and Bartlett's (Bartlett et al., 1954) test for factor analyses; the same could not be done for the m36 MCI group, as due to the lower frequency of symptoms and low sample size, the analysis was not computable.
Abbreviations: μ=mean, SD=standard deviation, F=female, M=male.

Table 2. Prevalence of neuropsychiatric symptoms at each time point.

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Delusions	Total	5.2%	8.3%	7.1%	4.5%	5.4%	8.8%	11.7%
	AD	10.6%	18.1%	17.7%	12.9%	13.2%	15%	16.4%
	MCI	2.4%	1.4%	1.8%	0.7%	1.7%	3.9%	5.0%
Hallucinations	Total	3.5%	4.3%	4.6%	6.0%	3.0%	2.7%	9.1%
	AD	7.2%	8.1%	9.3%	17.7%	7.5%	6.7%	18%
	MCI	1.5%	0.7%	2.3%	0.7%	0.9%	0%	0%
Agitation	Total	29.4%	30.0%	31.5%	36.5%	33.3%	34.3%	33.1%
	AD	26.1%	34.4%	42.1%	50.0%	48.1%	36.7%	39.3%
	MCI	25.8%	26.5%	26.3%	30.4%	26.1%	32.5%	26.7%
Depression	Total	47.4%	44.1%	42.3%	40.5%	41.1%	46.0%	48.8%
	AD	47.2%	45.0%	43.9%	48.4%	37.7%	46.7%	54.1%
	MCI	47.5%	42.8%	41.5%	37.0%	40.6%	45.5%	43.3%
Anxiety	Total	28.8%	31.3%	29.9%	32.5%	30.4%	30.7%	19.0%
	AD	33.3%	40.6%	39.3%	41.9%	37.7%	35.0%	18.0%
	MCI	26.4%	35.1%	25.3%	28.3%	37.0%	27.3%	20.0%
Elation	Total	3.7%	5.1%	5.6%	4.5%	4.8%	4.4%	2.5%
	AD	4.4%	6.9%	7.5%	1.6%	11.3%	10%	1.6%
	MCI	3.3%	2.8%	4.6%	4.3%	1.7%	0%	3.3%
Apathy	Total	45.0%	38.0%	32.1%	37.5%	30.4%	32.8%	34.7%
	AD	50.0%	56.9%	45.5%	51.6%	54.7%	45.0%	47.5%
	MCI	27.0%	26.5%	23.5%	31.2%	19.1%	33.4%	21.7%
Disinhibition	Total	18.0%	19.0%	19.1%	24.0%	23.2%	22.4%	2.04%
	AD	21.7%	21.2%	38.0%	33.9%	28.3%	26.7%	36.1%
	MCI	16.0%	16.5%	14.7%	19.6%	20.9%	19.5%	11.7%
Irritability	Total	38.4%	43.0%	41%	47.5%	41.7%	46.0%	57.9%
	AD	38.9%	42.5%	39.3%	48.4%	35.8%	41.7%	44.3%
	MCI	37.7%	42.4%	41.9%	47.1%	44.3%	49.4%	51.7%
Aberrant Motor Behaviour	Total	11.1%	14.1%	12.7%	12.0%	11.7%	18.2%	19%
	AD	17.8%	26.3%	26.2%	24.2%	18.9%	30.0%	27.9%
	MCI	5.9%	6.0%	6.0%	6.5%	7.0%	9.1%	10.0%
Sleep Disorder	Total	30.9%	32.2%	37.7%	37.5%	39.3%	36.5%	28.1%
	AD	22.8%	21.9%	31.8%	32.3%	35.8%	45.0%	27.9%
	MCI	35.3%	37.1%	40.6%	39.9%	40.9%	37.7%	28.3%
Appetite Disorder	Total	19.9%	26.0%	24.7%	22.5%	25.0%	29.9%	24.0%
	AD	28.4%	36.9%	41.1%	37.1%	42.4%	33.3%	24.6%
	MCI	14.8%	18.7%	16.6%	15.9%	16.5%	27.7%	23.3%

Notes. The percentages are reported to 1 decimal place.

Table 3. Average scores for the neuropsychiatric symptoms at each time point.

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Delusions	Total	3.5	3.6	3.6	3.4	4.7	2.5	3.2
	AD	4.1	4.2	3.1	2.8	5.8	2.7	3.7
	MCI	2.3	2.7	6.0	8.0*	1.0	1.6	2.6
Hallucinations	Total	2.1	2.0	3.2	1.7	4.0	2.5	2.7
	AD	2.0	2.8	2.5	1.5	4.7	2.5	2.7
	MCI	2.2	1.0	4.6	4.0*	1.0*	NA	NA
Agitation	Total	2.8	2.7	2.8	3.0	3.1	2.9	3.6
	AD	3.1	2.8	2.9	2.6	3.5	3.0	3.5
	MCI	2.6	2.6	2.8	3.2	2.7	2.8	3.8
Depression	Total	2.1	2.4	2.6	2.7	2.7	2.6	2.9
	AD	2.3	2.7	2.8	3.1	3.4	2.6	2.8
	MCI	2.0	2.2	2.5	2.4	2.5	2.7	2.9
Anxiety	Total	2.9	2.8	3.7	3.3	2.4	3.2	3.4
	AD	2.9	2.9	4.5	4.1	3.1	3.3	4.1
	MCI	2.9	2.8	3.0	2.7	2.7	3.1	2.7
Elation	Total	2.8	3.9	3.1	4.0	1.7	1.6	1.3
	AD	3.3	5.3	3.2	8.0*	1.5	1.6	2.0*
	MCI	2.4	3.3	3.0	3.3	2.5	NA	1.0
Apathy	Total	3.5	4.0	4.1	4.3	4.5	5.5	4.2
	AD	3.5	4.6	4.6	4.4	5.4	6.0	4.7
	MCI	3.5	3.3	3.6	4.2	3.4	4.9	3.1
Disinhibition	Total	2.4	2.5	2.3	3.4	2.2	3.2	2.4
	AD	2.4	3.0	3.0	4.0	2.5	3.2	2.6
	MCI	2.4	2.4	1.7	2.9	2.0	3.0	1.8
Irritability	Total	2.9	3.0	3.0	3.1	3.0	3.4	3.1
	AD	3.3	3.5	3.5	3.2	4.0	3.7	3.1
	MCI	2.7	2.7	2.8	3.0	2.7	3.2	3.1
Aberrant Motor Behaviour	Total	3.4	4.3	4.2	5.1	3.8	4.2	4.8
	AD	3.8	4.9	3.7	5.1	5.4	4.1	5.0
	MCI	3.7	3.5	5.3	5.2	2.5	4.5	4.1
Sleep Disorder	Total	3.8	4.0	3.9	4.1	4.7	4.0	4.8
	AD	3.2	4.6	4.4	5.1	6.7	4.0	5.0
	MCI	4.0	3.9	3.6	3.7	3.9	3.9	4.5
Appetite Disorder	Total	4.7	4.7	5.0	4.4	5.2	5.3	5.0
	AD	4.9	5.4	5.6	5.5	5.9	5.5	5.0
	MCI	4.5	4.3	4.3	3.3	4.5	5.2	5.0

Notes. The average scores reported here were calculated from the Total NPI Scores (range 1-12) for each Neuropsychiatric Symptom for each group at each time point. The total NPI scores for each symptom were calculated by multiplying the frequency scores (range 1-4) and severity scores (range 1-3) and reported to 1 decimal place. *These scores do not represent averages but the score of the only participant who presented that symptom at that time point.
NA: No participant presented that symptom at that time point.

Table 4. Average scores of Neuropsychiatric Symptoms across time including zero.

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Delusions	Total	0.18	0.30	0.25	0.15	0.25	0.21	0.66
	AD	0.43	0.76	0.55	0.37	0.77	0.41	0.60
	MCI	0.05	0.03	0.11	0.05	0.01	0.06	0.13
Hallucinations	Total	0.07	0.08	0.14	0.10	0.11	0.07	0.45
	AD	0.15	0.23	0.23	0.27	0.35	0.16	0.49
	MCI	0.03	0.01	0.10	0.02	0.01	NA	NA
Agitation	Total	0.83	0.81	0.90	1.10	1.04	1.00	1.63
	AD	1.13	0.98	1.22	1.33	1.75	1.11	1.37
	MCI	0.67	0.71	0.75	0.99	0.71	0.90	1.01
Depression	Total	1.01	1.06	1.12	1.10	1.14	1.24	1.58
	AD	1.12	1.23	1.23	1.51	1.30	1.23	1.55
	MCI	0.96	0.96	1.07	0.91	1.06	1.24	1.28
Anxiety	Total	0.84	0.89	1.11	1.08	0.88	0.99	1.05
	AD	0.98	1.20	1.80	1.74	1.18	1.26	0.75
	MCI	0.76	0.72	0.77	0.78	0.74	0.85	0.55
Elation	Total	0.10	0.19	0.17	0.14	0.08	0.07	0.06
	AD	0.15	0.36	0.24	0.12	0.16	0.16	0.03
	MCI	0.08	0.09	0.13	0.14	0.04	NA	0.03
Apathy	Total	1.20	1.52	1.34	1.62	1.38	1.83	2.00
	AD	1.77	2.65	2.32	2.27	2.96	2.70	2.27
	MCI	0.94	0.88	0.85	1.33	0.65	1.15	0.68
Disinhibition	Total	0.43	0.48	0.45	0.82	0.52	0.70	0.90
	AD	0.52	0.64	0.84	1.38	0.71	0.86	0.96
	MCI	0.38	0.40	0.26	0.57	0.43	0.58	0.21
Irritability	Total	1.11	1.30	1.25	1.46	1.27	1.56	1.72
	AD	1.28	1.51	1.38	1.56	1.45	1.55	1.40
	MCI	1.02	1.17	1.19	1.42	1.20	1.58	1.61
Aberrant Motor Behaviour	Total	0.38	0.60	0.53	0.62	0.44	0.78	1.48
	AD	0.67	1.30	0.97	1.24	1.01	1.25	1.40
	MCI	0.22	0.21	0.32	0.34	0.17	0.41	0.41
Sleep Disorder	Total	1.18	1.31	1.47	1.55	1.88	1.46	1.97
	AD	0.75	1.01	1.42	1.66	2.43	1.43	1.40
	MCI	1.41	1.48	1.49	1.50	1.62	1.49	1.30
Appetite Disorder	Total	0.94	1.24	1.25	1.01	1.32	1.60	1.84
	AD	1.45	1.99	2.32	2.06	2.56	1.83	1.22
	MCI	0.67	0.81	0.72	0.53	0.74	1.42	1.18

Notes. The score reported here are derived from the Total Score including the participants who scored 0, therefore reflect the severity of the symptoms at each

time point within all participants. (range 0-12).
NA: No participant presented that symptom at that time point.

Table 5. Principal Components Analysis and Principal Axis Factor Analysis on the total samples at all time points.

		PRINCIPAL COMPONENT ANALYSIS				FACTOR ANALYSIS			
Time point	**Variance**	**Component 1**	**Component 2**	**Component 3**	**Component 4**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Baseline	55%	Depression[1] Anxiety[1] Agitation[2] Irritability[2]	Elation[3] Disinhibition[3]	Apathy[5] Sleep[5] Appetite[5]	Delusions[4] Hallucinations[4]	Agitation[2] Irritability[2]	Elation[3] Disinhibition[3]	Apathy[5]	Depression[1] Anxiety[1]
Month 12	54%	Agitation[2] Anxiety[1] Irritability[2]	Delusions[4] Hallucinations[4] Apathy[5] Abm[5]	Elation[3] Disinhibition[3]	Depression[1] Sleep[5] Appetite[5]	Delusions[4] Agitation[2] Irritability[2]	Hallucinations[4] Abm[5]	Elation[3] Disinhibition[3]	Depression[1] Anxiety[1] Apathy[5]
Month 24	44%	Delusions[4] Hallucinations[4] Agitation[2] Depression[1] Anxiety[1] Irritability[2]	Elation[3] Disinhibition[3] Sleep[5] Appetite[5]	Apathy[5] Abm[5]		Delusions[4] Hallucinations[4] Depression[1] Anxiety[1]	Agitation[2] Irritability[2] Elation[3] Disinhibition[3]	Apathy[5] Appetite[5]	
Month 36	44%	Delusions[4] Hallucinations[4] Anxiety[1] Sleep[5]	Agitation[2] Disinhibition[3] Irritability[2] Abm[5]	Depression[1] Elation[3] Apathy[5] Appetite[5]		Agitation[2] Anxiety[1] Irritability[2]	Disinhibition[3] Abm[5]	Depression[1] Apathy[5] Appetite[5]	
Month 48	46%	Agitation[2] Depression[1] Anxiety[1] Elation[3] Disinhibition[3] Irritability[2]	Delusions[4] Hallucinations[4] Apathy[5] Sleep[5]	Abm[5] Appetite[5]		Agitation[2] Depression[1] Irritability[2]	Delusions[4] Apathy[5] Sleep[5]	Disinhibition[3] Abm[5]	
Month 60	47%	Agitation[2] Apathy[5] Disinhibition[3] Irritability[2]	Delusions[4] Elation[3] Appetite	Hallucinations[4] Depression[1] Anxiety[1] Sleep		Agitation[2] Apathy Disinhibition[3] Irritability[2]	Delusions[4] Elation[3] Appetite[5]	Depression[1] Anxiety[1]	
Month 72	40%	Delusions[4] Hallucinations[4] Anxiety[1] Abm[5] Sleep[5] Appetite[5]	Agitation[2] Depression[1] Disinhibition[3] Irritability[2]			Delusions[4] Hallucinations[4] Anxiety[1] Abm[5] Sleep[5]	Agitation[2] Disinhibition[3] Irritability[2]		

Notes. The factors are reported as extracted using Principal Axis Factoring extraction method, and Direct Oblimin rotation method; The Promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, these were reported according to the Direct Oblimin method. Abbreviations: Abm=aberrant motor behaviour. 1. Symptoms related to affect/mood; 2. Symptoms related to hyperactivity; 3. Symptoms related to impulse control and hypomania; 4. Psychotic symptoms; 5. Apathy/aberrant motor behaviour/neurovegetative functions.

Table 6. Principal Components Analysis and Principal Axis Factor Analysis on the AD samples at all time points available.

		PRINCIPAL COMPONENT ANALYSIS					FACTOR ANALYSIS				
Time point	**Variance**	**Component 1**	**Component 2**	**Component 3**	**Component 4**	**Component 5**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**
Baseline	64%	Agitation Irritability	Elation Disinhibition	Delusions Hallucinations Sleep	Apathy Appetite	Depression Anxiety Abm	Depression Anxiety	Elation Disinhibition	Delusions Hallucinations Sleep	Agitation Irritability	Apathy Appetite
Month 12	48%	Delusions Agitation Depression Anxiety Irritability	Elation Disinhibition Appetite	Hallucinations Apathy Abm Sleep			Delusions Agitation Depression Anxiety Irritability	Hallucinations Apathy Abm	Elation Disinhibition		
Month 24*	54%	Delusions Hallucinations Agitation Depression Anxiety Irritability	Elation Disinhibition Sleep Appetite	Apathy Abm			Delusions Hallucinations Agitation Depression Anxiety Irritability	Elation Disinhibition Sleep	Apathy Abm		

Notes. The factors are reported as extracted using Principal Axis Factoring extraction method, and Direct Oblimin rotation method; The Promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the Direct Oblimin method.

*This group had a ratio of less than 10:1 observation per variable (107 participants – 8.9:1).

Abbreviations: Abm=aberrant motor behaviour.

Table 7. Principal Components Analysis and Principal Axis Factor Analysis on the MCI samples at all time points available.

		PRINCIPAL COMPONENT ANALYSIS					FACTOR ANALYSIS				
Time point	**Variance**	**Component 1**	**Component 2**	**Component 3**	**Component 4**	**Component 5**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**
Baseline	47%	Agitation Disinhibition Irritability	Delusions Depression Anxiety	Elation Apathy Abm	Sleep Appetite		Agitation Disinhibition Irritability	Delusions Depression Anxiety	Elation Apathy Abm	Sleep Appetite	
Month 12	41%	Delusions Agitation Depression Anxiety Irritability	Elation Disinhibition Appetite	Hallucinations Apathy Abm Sleep			Agitation Disinhibition Irritability	Elation	Depression Apathy		
Month 24	59%	Agitation Elation Irritability	Depression Apathy	Sleep Appetite	Delusions Hallucinations Anxiety	Disinhibition Abm	Depression Apathy	Agitation Elation Irritability	Hallucinations Anxiety	Disinhibition Abm	Sleep Appetite
Month 36	49%	Hallucinations Anxiety Irritability Sleep	Delusions Depression Apathy Appetite	Agitation Elation Disinhibition Abm			Hallucinations Anxiety Irritability Sleep	Delusions Depression Apathy	Agitation Disinhibition Abm		

Notes. The factors are reported as extracted using Principal Axis Factoring extraction method, and Direct Oblimin rotation method; The Promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the Direct Oblimin method. The order of the symptoms within each factor reflects the loading size (higher contributions to the factor are first, in descending order).
Abbreviations: Abm=aberrant motor behaviour.

Supplementary Material

Figure S1. MMSE scores on the total sample, MCI, and AD samples.

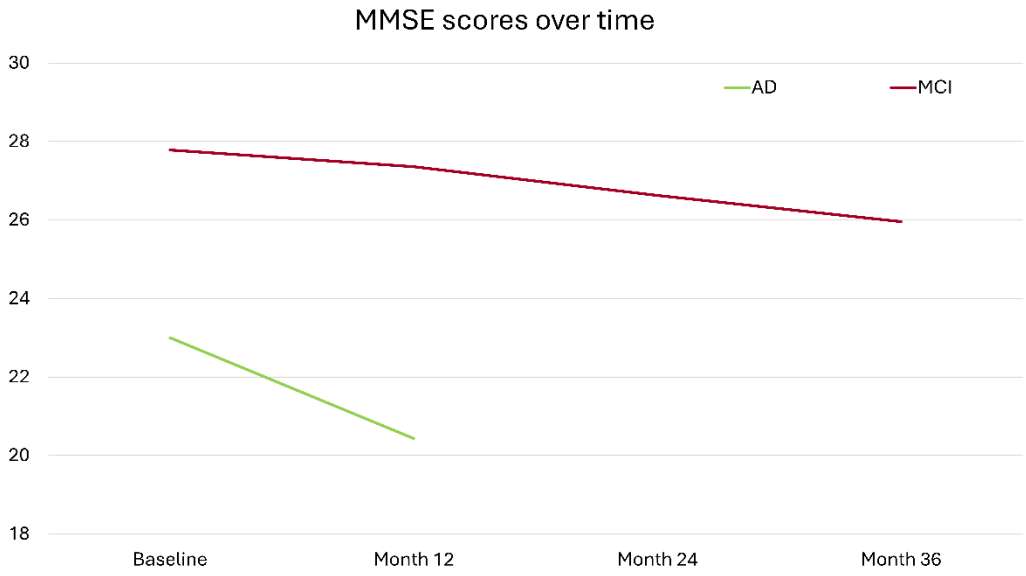


Table S1. Participants information.

Sample Size	Age (at baseline)	Gender	Education	MMSE (at baseline)
147 AD	μ=74.51 SD=7.94	F=57 M=90	μ=15.76 SD=2.60	μ=23.00 SD=2.29
190 MCI	μ=71.24 SD=7.14	F=82 M=108	μ=16.20 SD=2.67	μ=27.78 SD=1.88

Notes. Sample sizes do not change over time as the same sets of participants are tracked.
Abbreviations: μ=mean, SD=standard deviation, F=female, M=male.

Table S2. Prevalence of neuropsychiatric symptoms across time.

Symptom	Group	Baseline	Month 12	Month 24	Month 36
Delusions	AD	8.9%	17.0%	4.2%	4.2%
	MCI at Bl	2.1%	2.6%		
Hallucinations	AD	6.2%	7.4%	3.6%	6.3%
	MCI at Bl	1.0%	1.0%		
Agitation	AD	31.3%	30.6%	25.7%	26.3%
	MCI at Bl	15.7%	18.4%		
Depression	AD	38.7%	39.4%	33.1%	31.0%
	MCI at Bl	33.1%	32.1%		
Anxiety	AD	28.5%	36.0%	21.0%	21.5%
	MCI at Bl	15.2%	19.4%		
Elation	AD	3.4%	4.7%	3.6%	2.1%
	MCI at Bl	1.5%	1.0%		
Apathy	AD	44.8%	48.9%	26.3%	29.4%
	MCI at Bl	17.8%	24.7%		
Disinhibition	AD	20.4%	18.3%	12.6%	16.8%
	MCI at Bl	11.0%	11.0%		
Irritability	AD	34.0%	37.4%	31.0%	32.1%
	MCI at Bl	25.2%	28.9%		
Aberrant Motor Behaviour	AD	16.3%	25.8%	7.3%	10.0%
	MCI at Bl	2.6%	5.2%		
Sleep Disorder	AD	18.3%	17.6%	31.5%	28.9%
	MCI at Bl	26.3%	25.7%		
Appetite Disorder	AD	25.1%	31.9%	20.0%	15.2%
	MCI at Bl	9.4%	15.7%		

Notes. The percentages are reported to 1 decimal place.
Data was only reported for the time points used at each group (AD baseline and m12, MCI baseline, m12, m24 and m36).

Table S3. Average positive scores of neuropsychiatric symptoms across time.

Symptom	Group	Baseline	Month 12	Month 24	Month 36
Delusions	AD	4.53	4.60		
	MCI at Bl	3.00	2.00	4.37	3.12
Hallucinations	AD	2.55	3.54		
	MCI at Bl	3.50	1.00	3.28	1.75
Agitation	AD	3.08	3.22		
	MCI at Bl	2.90	2.54	3.36	3.10
Depression	AD	2.38	2.75		
	MCI at Bl	1.74	2.50	2.68	2.59
Anxiety	AD	2.85	2.94		
	MCI at Bl	3.20	3.16	3.55	3.17
Elation	AD	3.20	5.28		
	MCI at Bl	2.66	1.50	2.85	3.25
Apathy	AD	3.74	4.58		
	MCI at Bl	2.97	4.08	4.10	4.23
Disinhibition	AD	2.33	3.14		
	MCI at Bl	2.57	2.23	2.04	3.12
Irritability	AD	2.86	3.38		
	MCI at Bl	2.75	3.09	2.83	3.39
Aberrant Motor Behaviour	AD	4.04	4.84		
	MCI at Bl	4.60	3.50	4.00	4.52
Sleep Disorder	AD	3.40	4.46		
	MCI at Bl	4.18	4.26	4.30	4.52
Appetite Disorder	AD	4.97	5.17		
	MCI at Bl	4.33	4.60	4.97	4.51

Notes. The score reported here are derived from the Total Score (range 1-12) per each subscale of each Neuropsychiatric Symptom, which is calculated multiplying frequency scores (range 1-4) and severity scores (range 1-3). The average reported do not include the participants who scored 0, therefore only reflect the severity of the symptom within the percentage of participant who scored positively at that time point.
Data was only reported for the time points used at each group (AD baseline and m12; MCI baseline, m12, m24 and m36).

Table S4. Average scores of neuropsychiatric symptoms across time including zero.

Symptom	Group	Baseline	Month 12	Month 24	Month 36
Delusions	AD	0.40	0.78		
	MCI at Bl	0.06	0.05	0.18	0.13
Hallucinations	AD	0.15	0.26		
	MCI at Bl	0.03	0.01	0.12	0.11
Agitation	AD	0.96	0.98		
	MCI at Bl	0.45	0.46	0.86	0.81
Depression	AD	0.92	1.08		
	MCI at Bl	0.57	0.80	0.88	0.80
Anxiety	AD	0.81	1.06		
	MCI at Bl	0.48	0.61	0.74	0.68
Elation	AD	0.10	0.25		
	MCI at Bl	0.04	0.01	0.10	0.06
Apathy	AD	1.68	2.24		
	MCI at Bl	0.53	1.01	1.07	1.24
Disinhibition	AD	0.47	0.57		
	MCI at Bl	0.28	0.24	0.25	0.52
Irritability	AD	0.97	1.26		
	MCI at Bl	0.69	0.89	0.87	1.08
Aberrant Motor Behaviour	AD	0.65	1.25		
	MCI at Bl	0.12	0.18	0.29	0.45
Sleep Disorder	AD	0.62	0.78		
	MCI at Bl	1.10	1.10	1.35	1.31
Appetite Disorder	AD	1.25	1.65		
	MCI at Bl	0.41	0.72	0.99	0.68

Notes. The score reported here are derived from the Total Score including the participants who scored 0, therefore reflect the severity of the symptoms at each time point within all participants (range 0-12).
Data was only reported for the time points used at each group (AD baseline and m12; MCI baseline, m12, m24 and m36).

Table S5. Principal Components Analysis and Principal Axis Factor Analysis on the AD samples at all time points available.

		PRINCIPAL COMPONENT ANALYSIS				FACTOR ANALYSIS			
Time point	**Variance**	**Component 1**	**Component 2**	**Component 3**	**Component 4**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Baseline	59%	Agitation Depression Anxiety Irritability Abm	Elation Disinhibition	Apathy Sleep Appetite	Delusions Hallucinations	Agitation Depression Anxiety Irritability	Elation Disinhibition	Hallucinations	Apathy
Month 12	58%	Delusions Agitation Elation Disinhibition Irritability	Hallucinations Apathy Abm	Depression Anxiety	Sleep Appetite	Delusions Agitation Irritability	Hallucinations	Depression Anxiety	Apathy Sleep Appetite

Notes. The factors are reported as extracted using Principal Axis Factoring extraction method, and Direct Oblimin rotation method; The Promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the Direct Oblimin method.
Abbreviations: Abm=aberrant motor behaviour.

Table S6. Principal Components Analysis and Principal Axis Factor Analysis on the MCI samples at all time points available.

			PRINCIPAL COMPONENT ANALYSIS					FACTOR ANALYSIS				
Time point	**%MCI/AD**	**Variance**	**Component 1**	**Component 2**	**Component 3**	**Component 4**	**Component 5**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**
Baseline	MCI 100%	55%	Agitation Irritability	Delusions Depression	Anxiety Elation Disinhibition Abm	Sleep Appetite		Anxiety Elation Apathy Disinhibition	Delusions Depression	Sleep Appetite	Agitation Irritability	
Month 12	MCI 88% AD 12%	54%	Depression Apathy Appetite	Agitation Disinhibition Irritability Abm	Anxiety Elation Sleep	Delusions Hallucinations		Apathy Appetite	Agitation Disinhibition Abm	Depression Anxiety	Irritability	
Month 24	MCI 75% AD 25%	56%	Hallucinations Agitation Anxiety Irritability	Depression Apathy	Elation Disinhibition Abm	Sleep Appetite		Depression Apathy Appetite	Agitation Irritability	Abm	Hallucinations Anxiety	
Month 36	MCI 68% AD 32%	66%	Agitation Irritability	Depression Appetite Sleep	Hallucinations Anxiety Abm	Elation Disinhibition	Delusions Apathy	Depression Appetite	Elation Disinhibition	Hallucinations Anxiety	Agitation Irritability	Delusions

Notes. The factors are reported as extracted using Principal Axis Factoring extraction method, and Direct Oblimin rotation method; The Promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the Direct Oblimin method.
Abbreviations: Abm=aberrant motor behaviour.