Quali-quantitative assessment of self-reported cognitive difficulties in non-demented elders: association with medical help seeking, cognitive deficits and beta-amyloid imaging

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La Joie et al, accepted on Dec 5th, 2016
Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring.

Qualitative and quantitative assessment of self-reported cognitive difficulties in non-demented elders: association with medical help seeking, cognitive deficits and beta-amyloid imaging

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Word count: 3,697/3,500 words (exclusive of abstract, references, tables, & figures)

Figures and Tables: 6/6 (4 Figures, 2 Tables)

References: 51/50

Supplementary Material: 3 methods sections, 2 figures, 7 Tables.

Keywords. Subjective Cognitive Decline; Memory Complaint, beta-amyloid; positron emission tomography; preclinical; biomarkers; anosognosia; prodromal Alzheimer's Disease; mild cognitive impairment; orientation.

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Abstract (150/150 words)

Introduction. Subjective cognitive decline (SCD) could help identify early stages of Alzheimer's disease. However, SCD is multidetermined and protean, and the type of cognitive complaint associated with preclinical Alzheimer's needs refinement.

Methods. 185 Non-demented elders recruited from either the community or from a memory clinic filled out a questionnaire. We searched for item responses associated with medical help-seeking, cognitive deficits, and β-amyloidosis.

Results. Compared to community-recruited controls (n=74), help-seeking patients reported a stronger multidomain SCD that was mostly unrelated to the presence of detectable cognitive deficits. Only a few items, notably assessing temporal disorientation, distinguished help-seeking patients with (n=78) or without (n=33) memory deficits. Associations between SCD and β-amyloidosis were not restricted to the memory domain and varied across clinical stages.

Conclusion. Detailed evaluation of SCD could provide accessible indication of the presence of β-amyloid or cognitive deficits, which might prove useful for early diagnosis and clinical trial enrichment strategies.

Research In Context (147/150 words)

Systematic review. The authors recently reviewed the literature on SCD and AD neuroimaging biomarkers (doi:10.1016/j.jalz.2016.08.011). The present work falls within the framework defined by the SCD-initiative (doi: 10.1016/j.jalz.2014.01.001) and addresses questions raised in a recent overview of questionnaires currently used to assess SCD in preclinical AD (doi:10.3233/JAD-150154).

Interpretation. SCD endorsement was strongly related to medical help seeking while more subtle nuances, notably related to self-reported temporal disorientation, were specifically associated with objectively detectable memory deficits. The presence of Aβ was associated with different patterns of SCD beyond memory complaint in both healthy controls and patients with MCI.

Future directions. Our data reinforces the need to consider subjective cognition at large rather than a more specific memory complaint to detect early AD. Pending replication, these results could help improve enrichment strategies to screen for relevant candidates for anti-amyloid trials conducted in preclinical and prodromal stages.

1. Introduction

1.1. General background and previous studies

The subjective feeling of cognitive decline (SCD) has been suggested as a potential early indicator of ongoing neurodegenerative processes for decades [1,2]. Indeed, self-reported cognitive complaint was implemented in the criteria for Mild Cognitive Impairment [3] that have been widely used to study the prodromal stage of Alzheimer's disease (AD). More recently, in line with the growing interest for defining and characterizing preclinical stages of AD [4,5], researchers have assessed SCD in individuals without measurable cognitive deficits, i.e. cognitively "normal" older adults. Indeed, longitudinal investigations have repeatedly shown that SCD is associated with an increased risk of subsequent cognitive decline and conversion to dementia [6]. In addition, cross-sectional studies have shown that the presence or severity of SCD is related to abnormal neuroimaging biomarkers suggestive of underlying AD pathophysiological processes [7,8]. SCD has notably been associated with the presence of β-amyloidosis (Aβ) evidenced using positron emission tomography (PET) in several independent samples of cognitively normal elders [8–12].

Altogether, converging evidence indicates that SCD might be among the first clinically observable signs of AD and could potentially be used as a screening tool for enrichment strategies for clinical trials [7,12,13]. The development of affordable and easily accessible measures that could help predict the presence of Aβ is needed to reduce the resources, time, and costs associated with the selection of appropriate candidates for clinical trials targeting Aβ [14]. This is becoming particularly important as the field is moving toward interventions in prodromal [15] or even preclinical AD [16] populations, in which the prevalence of Aβ is at most moderate [17].

However, associations between SCD and AD biomarkers were not identified in all studies (see [8] for review), illustrating that SCD is multidetermined [18,19] and loosely defined. Indeed, definitions or criteria used to define SCD widely vary across labs, hampering the direct comparison between results from different groups. For these reasons, the international SCD-Initiative (SCD-I) was recently formed to stimulate standardized research and refine our understanding of SCD in the context of early AD [20,21]. One of the main aims highlighted in the SCD-I framework is the identification of the specific features of SCD that increase the likelihood of underlying preclinical AD.

We recently showed that different approaches to defining and studying SCD led to different associations with AD biomarkers and affective symptomatology [8]. More specifically, Aβ was associated with higher levels of self-reported cognitive difficulties assessed through a questionnaire, but was not related to medical help-seeking *per se*: asymptomatic memory clinic attendees did not have more Aβ than community-recruited individuals with similar levels of self-reported cognitive difficulties.

Over and above the recruitment setting, quantification of SCD also varies greatly across groups: members of the SCD-I systematically compared questionnaires used in 19 international studies [22], and showed little overlap among measures (item phrasing, number of items, response options, etc.). Authors encouraged researchers to identify specific and relevant items, notably by assessing their relationships to AD biomarkers.

1.2. Overview and aims of the present study

Following these recommendations, we aimed at better characterizing the relevance of different types of self-reported cognitive difficulties to identify early AD stages in non-demented older adults. We studied three groups of individuals: 1) healthy aged subjects recruited from the community (HAS), 2) patients who sought help at a memory clinic because of concerns about their memory but whose clinical and neuropsychological examination did not show any deficit (SCDclinic), 3) patients who sought help at a memory clinic because of concerns about their memory and who actually fulfilled criteria for amnestic Mild Cognitive Impairment (aMCI).
All participants filled out a standardized SCD questionnaire, the Cognitive Difficulties Scale (CDS [23]), which covers multiple cognitive domains. First, the questionnaire was analyzed to identify patterns of responses that were specifically associated 1) with medical-help seeking in cognitively normal individuals (SCDclinic>HAS), or 2) with the presence of detectable episodic memory deficits (aMCI>SCDclinic). Second, we searched for associations between patterns of responses and the presence of Aβ deposition, assessed using Florbetapir-PET.
For the sake of completeness, the CDS was analyzed in two complementary ways. Analyses were first performed for each item separately using non-parametric tests. Then, exploratory factor analysis was conducted to reveal latent variables and to obtain more reliable estimates of different aspects of SCD by grouping highly-correlated items.

2. Methods

2.1. Participants

The participants included in the current paper were drawn from from two academic studies conducted by the same investigators: the IMAP+ study [8,24–27] and an earlier study of patients with aMCI [28]. All participants were aged 55 years or older.
The control group (HAS) included volunteers to our academic study on aging and AD and were recruited through advertising in local media and word-of-mouth. Only those volunteers who had never consulted a memory clinic and showed normal neuropsychological examination (ie. scores within the normal range) were included.
Patients with SCDclinic and aMCI were recruited from local memory clinics they had visited due to memory concerns. During the screening interview, the clinician ensured

that the complaint was not related to current medication, major psychiatric or neurological conditions (including major depressive disorder), or other medical conditions. For this specific study, we only selected non-demented individuals and classified them as SCDclinic or aMCI depending on the results of their cognitive assessment. SCDclinic had no "objective" evidence for impaired cognition (i.e. they scored within the normal range on all tests) while aMCI patients had detectable episodic memory deficits, i.e. at least one score below the 5th percentile using adapted norms on the Free and Cued Selective Reminding Test (FCSRT) [29].
The two studies were approved by local ethical committees, and all participants gave written consent before undergoing further investigation including quantification of SCD, detailed neuropsychological assessment, and neuroimaging MRI and PET scans. Demographics are provided in ***Table 1***.

----------**Table 1** around here ----------

2.2. Neuropsychological Evaluation

2.2.1. Self-reported Cognitive Difficulties

Self-reported cognitive difficulties were assessed using the Cognitive Difficulties Scale [23], a 39-item questionnaire that requires participants to rate how often they currently experience cognitive difficulties in everyday life using a 5-point scale (from "never" = 0, to "very often" = 4). The 39 items, detailed in ***Table 2***, cover a large span of domains (retrospective and prospective memory, attention, language, orientation, praxis, etc.), and previous independent studies have confirmed the multidimentionality of the scale [30,31]. The questionnaire was not part of the screening process and was acquired once participants were already classified into one of the three clinical groups. It should also be highlighted that the questionnaire was filled out by the participants alone (without any intervention from the experimenter) and that none of the participants knew their APOE genotype or Florbetapir status when enrolling in the study.

----------**Table 2** around here ----------

2.2.2. Standardized measures of cognition

Participants underwent an extensive neuropsychological evaluation. To obtain robust proxies of cognitive abilities, composite scores were created for executive functions, verbal abilities, and episodic memory. Not that the latter was calculated without using FCSRT scores to avoid circularity as this test was used as an inclusion criteria and was therefore normal in all HAS and SCDclinic but low in aMCI (see ***Table 1***). For all composite scores, only scores showing no ceiling or floor effects were used and higher values indicate better performances (see S***upplementary Methods*** for further detail).

Depressive symptomatology was assessed using the Montgomery-Asberg depression rating scale (MADRS).

2.3. Neuroimaging measures

A subset of 151 participants (68 HAS, 33 SCDclinic, 50 aMCI) underwent both structural magnetic resonance imaging (MRI) and positron emission tomography (PET) with Florbetapir. Details on image acquisition and preprocessing are available in previous publications [8] and in the ***Supplementary Methods***. Briefly, PET images were preprocessed using MRI data for partial volume effect correction and extraction of individual uptake values in a predetermined neocortical mask [25,31]. Participants were classified as Aβ-positive or Aβ-negative based on Florbetapir-PET data acquired in a group of 41 healthy adults below 40 years old [8,26,32].

2.4. Statistical analyses

2.4.1. Item-by-item analyses

Analyses were first conducted item-by-item to identify the responses showing a significant clinical group difference; non-parametric tests were applied because of the ordinal nature of the dependent variables [33]. Kruskal-Wallis tests were first used to identify the effect of clinical group; when significant using a stringent Bonferroni correction ($\alpha < 0.001282 = 0.05/39$), Mann-Whitney tests were used for pairwise comparisons. In order to limit multiple testing, post-hocs were limited to the two contrasts of interest, i.e. to identify items that were related to medical help seeking (HAS versus SCDclinic) or cognitive impairment (SCDclinic versus aMCI). Bonferroni correction was applied at this step as well to define statistical significance ($\alpha < 0.025 = 0.05/2$). In a second set of analyses, we tested for associations between item endorsement and Aβ status using Mann-Whitney tests. Lastly, we assessed correlations between item endorsement and cognitive or affective measures using non-parametric Spearman correlation coefficients.

2.4.2. Exploratory Factor analysis (EFA)

EFA was conducted using the freely available FACTOR package (http://psico.fcep.urv.es/utilitats/factor/). This choice was motivated by the optimal implementation of both polychoric correlations and parallel analysis. Resulting SCD factors were rotated using the oblique promin method, allowing factors to be inter-correlated. FACTOR methods were described in details elsewhere [34] and in the ***Supplementary Methods***. Factor scores were extracted for each participant to be used in subsequent analyses. These SCD factor scores, which have a continuous distribution, were analyzed using parametric statistics, enabling to test for both main effects and interactions with between (clinical group, Aβ status) and within subject (SCD factor) factors.

3. Results

3.1. Description of clinical groups

Group description is available on Table 1. On average, patients with aMCI were slightly older, less educated and more likely to carry the APOE ε4 allele than the other two groups. Per inclusion criteria, patients with aMCI had lower FCSRT scores than HAS and SCDclinic, and this difference was observed for all FCSRT subscores. Contrastingly, the SCDclinic group did not show any significant difference on any FCSRT subscore compared to the HAS group. The same pattern was observed with the three independent composite scores, with aMCI performing lower than the other two groups while HAS and SCDclinic had very comparable distributions (see ***Supplementary Figure 1***). Contrastingly, both the SCDclinic and aMCI groups had increased levels of SCD endorsement (measures on the total CDS score), and subclinical depressive symptomatology compared to HAS.

3.2. Factorial structure of the CDS

Analysis of the polychoric correlation matrix confirmed the suitability of the data for factor analysis: the Kaiser-Meyer-Olkin Index value was .898 and the Bartlett Sphericity test was highly significant (Chi-square=2935.3, df=595, p<.001). Parallel analysis recommended the extraction of three factors accounting for 46.4% of total variance, and resulting model showed a good fit of data (Goodness of Fit Index=0.98, Root Mean Square of Residual= .0505). The rotated factor loading matrix is presented in **Table 2**. SCD Factor 1 (eigenvalue=11.70, 33.4% of variance) had strong factor loadings on items related to attention and language, SCD factor 2 (eigenvalue=2.45, 7.0% of variance) was driven by items on orientation and memory (including both prospective and retrospective memory), while SCD factor 3 (eigenvalue=2.07, 5.9% of variance) corresponded to praxis and domestic activities.
Demographic variables were not associated with these SCD factor scores in any group (see ***Supplementary Table 1***) and were not included in the statistical models.

3.3. Patterns of SCD in clinical groups

3.3.1. item-by-item analysis

Item endorsement is visually presented on ***Figure 1***, ***Supplementary Figure 2*** and further described in the ***Supplementary Table 2***.

----------**Figure 1** around here ----------

Out of the 39 items included in the questionnaire, 16 (41%) showed significant between-group differences when applying a stringent Bonferroni correction (α=0.001282), 9

(23%) additional items were only significant at an uncorrected α=0.05, while 14 (36%) did not show a significant effect of clinical group using Kruskall-Wallis test (see ***Supplementary Table 3*** for further statistical details). Post-hoc tests were conducted in the 16 significant items; most (11) of them were significant in the medical help-seeking contrast (HAS < SCDclinic). These items mainly related to retrospective (e.g. 2, 9, 11) and prospective (e.g. 4, 6, 8) aspects of memory, as well as attentional processes (e.g. 3, 19). Contrastingly, only four items were associated with the presence of memory deficits in patients consulting at a memory clinic (SCDclinic < aMCI). Two of these items assessed temporal disorientation (items 21 and 38, "*I forget what day of the week/month it is*"), one assessed semantic memory (item 1 "*I have trouble recalling frequently used phone numbers*") and the last one referred to a feeling of a "blank mind" (item 37). It is to note that no item showed an unexpected gradient (higher endorsement in SCDclinic compared to HAS, or in aMCI compared to SCDclinic).
Overall, these analyses suggested that item endorsement was strongly associated to medical help-seeking and that a more subtle pattern was related to the presence of detectable memory deficits.

3.3.2. SCD factor scores

Analysis of SCD factor scores confirmed this pattern: the clinical group*SCD factor interaction was highly significant ($F(4, 364)=11.33$, $p<.001$), indicating that group differences were not identical for the three SCD factors. Post hoc testing (see ***Figure 2*** and ***Supplementary Table 4***) showed that SCD Factor 1 was elevated in both memory clinic groups (SCDclinic and MCI) compared to controls but was very comparable in the two patient groups (Cohen's d: 0.09, $IC_{95\%}$ [-0.27, 0.31]). SCD Factor 2 showed a different pattern with an incremental increase from HAS to aMCI, all between-group differences being statistically significant. Lastly, SCD Factor 3 did not significantly differ between groups.

----------**Figure 2** around here ----------

3.4. Association with Aβ status

Because of the small sample size in the SCDclinic group (9 Aβ-positive (28%), 18 Aβ-negative) compared to the other two groups (HAS: 19 Aβ-positive (33%), 49 Aβ-negative; aMCI: 35 Aβ-positive (70%), 15 Aβ-negative), the analyses were restricted to HAS and aMCI groups to avoid unbalanced statistical power.

----------**Figure 3** around here ----------

3.4.1. Item-by-item analyses

In HAS, we observed a general trend for stronger item endorsement on almost all items in individuals harboring Aβ deposits, compared to Aβ-negative participants (see ***Figure***

3, top left panel, and ***Supplementary Table 5***). Although no difference was significant using a stringent Bonferroni correction, 10 items had uncorrected p values < 0.05. These items spanned a broad range of cognitive domains including memory (eg. 9 "*I have trouble recalling names of people I know*", 32 "*I forget right away what people say to me*", 26 "*I need to have instructions repeated several times*") and attention (eg. 10 "*I find it hard to keep my mind on a task or a job*", 19 "*I lose my train of thought when I listen to somebody else*", 25 "*I cannot keep my mind on one thing*").
In aMCI, 5 items showed association with Aβ status, although not surviving Bonferroni correction. Interestingly, except for item 9, there was no overlap with the significant items identified in HAS; also, the direction of the association with Aβ was variable (see ***Figure 3***, bottom left panel, and ***Supplementary Table 6***). On the one hand, 3 items related to semantic memory or language were more endorsed by Aβ-negative patients than Aβ-positive patients (9 "*I have trouble recalling names of people I know*", 13 "*I fail to recognize people I know*", 15 "*I have trouble finding the name of objects*"). The opposite contrast (higher endorsement in Aβ-positive patients) was only found for the two temporal orientation items (items 21 and 38 "*I forget what day of the week/month it is*").

3.4.2. SCD factor scores

Further analyses were performed using SCD factor scores to confirm that the presence of Aβ modified the SCD pattern in a clinical group-dependent manner, as suggested by the item-by-item investigations. These analyses only included SCD factors 1 and 2 (as factor 3 did not differ between clinical groups and was of little relevance, being mainly driven by praxis-related items).
Indeed, in a full statistical model, the triple (clinical group*Aβ status*factor) interaction was significant ($F(1, 114)=9.00$, $p=.003$), confirming that Aβ was not associated with the same SCD pattern in the two groups. Subsequent analyses in the HAS group showed a main effect of Aβ status (Aβ-positive individuals showing increased SCD factor scores) but no Aβ status*factor interaction (See ***Figure 3***, top right panel). Contrastingly, only the Aβ status*factor interaction was significant in the aMCI group, with post hoc tests showing that Aβ-positive aMCI patients had lower scores than their Aβ-negative counterparts on the SCD factor 1 (See ***Figure 3***, bottom right panel).

3.5. Association with cognitive measures

For each clinical group, correlations were assessed between responses on each item and each composite cognitive score (***Figure 4***, left panel and ***Supplementary Table 7***). Globally, results show that significant correlations with cognitive scores were very sparse, and were found in both positive and negative directions. Analysis conducted with SCD factor scores 1 and 2 confirmed this pattern (***Figure 4***, right panel): SCD was poorly correlated to cognitive scores, except for a mild association between SCD factor 1 with verbal abilities restricted to aMCI.

----------**Figure 4** around here ----------

4. Discussion

Consistent with the growing interest of studying SCD in early stages of AD, and in line with the framework defined by the SCD-I, the present study aimed at refining our knowledge on SCD in non-demented elders. More precisely, we searched for specific self-reported cognitive difficulties associated with clinical features and Aβ imaging. To address these questions, we benefited from 1) using a questionnaire spanning multiple relevant cognitive domains and 2) including three groups of non-demented elders. This design allowed to distinguish correlates of medical help-seeking (community-recruited HAS versus SCDclinic) and detectable memory impairment (SCDclinic versus aMCI).

4.1. Patterns of SCD in clinical groups

Clinical group comparisons revealed a pattern that was consistent when considering items separately or using SCD factor scores. Globally, responses of the SCDclinic group were closer to aMCI than HAS, suggesting that item endorsement was more influenced by the recruitment setting than by the presence of detectable memory impairment. Previous reports have also shown that medical help-seeking is associated with a marked and generalized SCD [35–37], with a large overlap of global scores between asymptomatic and impaired patients [38,39]. In addition, a few studies have used a more quali-quantitative approach, assessing different SCD items in aMCI and SCDclinic groups. In these studies, questionnaires were centered on subjective memory difficulties and showed no [40] or subtle [41] group differences. Our findings are consistent, but also expand these previous works: three out of four items that differed between aMCI and SCDclinic groups were not memory-related. Thus, self-reports of temporal disorientation and "blank mind" were specifically significantly elevated in aMCI. The subjective temporal disorientation is a robust finding (both items survived stringent multiple testing correction) and echoes clinical studies suggesting that objectively measured disorientation correlates with episodic memory deficits and indicates a higher risk for subsequent cognitive decline [42]. Lastly, both pathology [43] and neuroimaging [42,44] investigations showed that, in AD, temporal disorientation was related to neurodegeneration in the hippocampal regions and posterior association cortices. Although while memory complaint itself is multidetermined and poorly specific to early AD, the co-occurrence of self-reported temporal disorientation and memory difficulties may provide converging evidence that the AD-sensitive hippocampo-parietal network [27,45] is dysfunctional, increasing the likelihood of underlying AD etiology.

4.2. SCD and Aβ

Associations between Aβ and SCD varied across domains and clinical stages. In community-recruited controls, we replicated previous findings [9–12] showing higher SCD in Aβ-positive individuals. Interestingly, this relationship was not specific to self-reported memory difficulties; it was also found for language and attention items (see items 19 and 31, as well as SCD factor 1). While the majority of questionnaires currently in use are centered on memory complaints [22], our finding reinforces the importance of considering subjective cognition at large rather than focusing only on memory complaints, as suggested by the SCD-I [20,22].
In aMCI, a reverse association was found (less SCD in Aβ-positive patients), especially on language items and factor scores. This might reflect the fact that Aβ-positive aMCI could actually have less language impairment than their Aβ-negative counterparts, but previous independent studies have not found such differences [46,47]. Alternatively, the lower language SCD in Aβ-positive patients might be due to anosognosia. This would be consistent with the previous finding that an AD profile of cerebrospinal fluid biomarkers was associated with an underestimation of language difficulties in aMCI [48]. Future analyses of the neuropsychological and neuroimaging profiles of our patients with aMCI will help address these hypotheses. Interestingly, Aβ was associated with higher endorsement in both temporal orientation items. However, these differences did not survive Bonferroni correction and were not reflected in the factor analyses, since orientation items were grouped with memory items.

4.3. Limitations, conclusions and perspectives

Our study has limitations. First, our questionnaire assessed current cognitive difficulties rather than feeling of decline over time, which might be more sensitive to detect AD-related SCD. Moreover, other potentially important features of SCD highlighted by the SCD-I (corroboration by informant, associated concern, etc.) were not assessed here and should be investigated. In addition, patients were recruited from our regional university hospital, which might constitute a selection bias and prevent generalization to all medical help-seeking patients. Indeed, patients' cognitive complaints were likely considered serious enough by their primary care physicians to be referred to our center. Also it should be noted that additional complementary statistical approaches could be used to identify the most relevant items or combination of items, using logistic regression [49] or item response theory [50,51]. Although interesting, the latter was not adapted to our goal (assessing different aspects of SCD) as it relies on the assumption that the questionnaire is unidimensional. Lastly, it should be noted that, although we used advanced EFA methods on the CDS questionnaire, our sample size (n = 185) is limited, and likely underpowered to optimally analyze the factorial structure of the CDS; replication in larger sample is therefore warranted to confirm and expand these results. Overall, this report confirms the interest of studying SCD in non-demented elders, and points to the relevance of assessing SCD beyond the memory domain. Subtle temporal

disorientation seems particularly interesting in a clinical setting: corresponding items were associated with the presence of both detectable memory deficits and amyloidosis. Future studies are needed to replicate and expand our findings, for example with additional AD biomarkers or through a longitudinal design, and with larger samples, especially in the SCDclinic group.

5. Acknowledgements

The authors thank J. Gonneaud, R. De Flores, J. Mutlu, B. Landeau, G. Poisnel, M. Leblond, T. Anquetil, K Mevel, N. Villain, M. Fouquet, A. Quillard, C. Schupp, J. Dayan, A. Chocat, L. Barre, A. Manrique, and the Cyceron MRI-PET staff members for their help with data acquisition. We are grateful to Adrienne Visani, Jacob Vogel, Alexandre Bejanin and Eider Arenaza-Urquijo for their insightful comments, and to the participants of the IMAP+ study.

Potential conflicts of interest. Dr Perrotin now works for Piramal Imaging Ltd. None of the other authors report any conflict of interest.

Sources of funding and support. The study was supported by Fondation Plan Alzheimer (Alzheimer Plan 2008-2012); Programme Hospitalier de Recherche Clinique (PHRCN 2011-A01493-38 and PHRCN 2012 12-006-0347); Agence Nationale de la Recherche (LONGVIE 2007); Région Basse-Normandie; Association France Alzheimer et maladies apparentées AAP 2013. Funding sources were not involved in the study design, data acquisition, data analysis, or manuscript writing. The first author had full access to the data and takes responsibility for the integrity of data analysis.

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Table 1. Group description

	HAS (n=74)	SCDclinic (n=33)	aMCI (n=78)	F and p values	effect size	pairwise comparisons
Age (years)	69 ± 7.2 [63, 68.5, 73]	68 ± 7.3 [63, 68, 72]	**73 ± 7.2** **[68, 73, 78]**	F(2, 182) = 7.36 p < .001	η^2 = .07	aMCI>HAS** aMCI>SCDclinic**
Female: n	40 (54%)	14 (42%)	38 (49%)	Fisher's exact test, p=.53		
Education (years)	12 ± 3.9 [9, 12, 15]	13 ± 3.5 [10, 14, 15]	**11 ± 3.6** **[7, 10, 14]**	F(2, 179) = 5.65 p = .004	η^2 = .06	HAS>aMCI* SCDclinic>aMCI**
MMSE (/30) #	29 ± 1.2 [28, 29, 30]	29 ± 1.1 [28, 29, 30]	**27 ± 1.7** **[26, 27, 28]**	F(2, 180) = 42.85 p < .001	η^2 = .32	HAS>aMCI*** SCDclinic>aMCI***
FCSRT (/48) # sum of 3 free recalls	30 ± 5.2 [26, 30, 33]	31 ± 5.9 [27, 29, 36]	**17 ± 6.4** **[11, 17, 21]**	F(2, 176) = 117.08 p < .001	η^2 = .57	HAS>aMCI*** SCDclinic>aMCI***
FCSRT (/48) # sum of 3 total recalls	46 ± 2.1 [45, 47, 48]	47 ± 1.8 [45, 47, 48]	**36 ± 7.8** **[30, 37, 43]**	F(2, 176) = 81.70 p < .001	η^2 = .48	HAS>aMCI*** SCDclinic>aMCI***
FCSRT (/16) # delayed free recall	12 ± 2.3 [10, 12, 14]	12 ± 2.2 [10, 12, 13]	**5 ± 3.6** **[2, 6, 8]**	F(2, 179) = 120.89 p < .001	η^2 = .57	HAS>aMCI*** SCDclinic>aMCI***
FCSRT (/16) # delayed total recall	15.7 ± 0.6 [16, 16, 16]	15.7 ± 0.5 [15, 16, 16]	**12 ± 3.6** **[10, 12.5, 15]**	F(2, 176) = 61.01 p < .001	η^2 = .41	HAS>aMCI*** SCDclinic>aMCI***
FCSRT (/16) # recognition	15.9 ± 0.3 [16, 16, 16]	15.9 ± 0.4 [16, 16, 16]	**14.8 ± 1.6** **[14, 15, 16]**	F(2, 173) = 24.85 p < .001	η^2 = .22	HAS>aMCI*** SCDclinic>aMCI***
Verbal abilities Composite score	0.32 ± 0.89 [-0.21, 0.32, 0.80]	0.39 ± 0.75 [-0.24, 0.24, 0.94]	**-0.65 ±0.94** **[-1.42, -0.49, 0.01]**	F(2, 155) = 24.72 p < .001	η^2 = .28	HAS>aMCI*** SCDclinic>aMCI***
Executive function Composite score	0.28 ± 0.76 [-0.08, 0.35, 0.76]	0.47 ± 0.83 [0.05, 0.39, 0.95]	**-0.59 ± 1.07** **[-1.20, -0.70, 0.04]**	F(2, 161) = 22.10 p < .001	η^2 = .22	HAS>aMCI*** SCDclinic>aMCI***
Episodic Memory Composite score	0.57 ± 0.69 [0.13, 0.64, 1.06]	0.37 ± 0.81 [-0.08, 0.31, 0.94]	**-0.90 ± 0.73** **[-1.44, -1.00, -0.46]**	F(2, 161) = 77.58 p < .001	η^2 = .49	HAS>aMCI*** SCDclinic>aMCI***
Depression # MADRS total score	0.8 ± 1.9 [0, 0, 1]	**3.4 ± 3.0** **[1.5, 2.5, 5]**	**3.8 ± 5.4** **[0, 2, 5]**	F(2, 153) = 12.47 p < .001	η^2 = .14	SCDclinic>HAS*** aMCI>HAS***
SCD CDS total score	40 ± 17 [29, 39.5, 50]	**57 ± 22** **[41, 55, 70]**	**60 ± 20** **[45, 57, 73]**	F(2, 182) = 21.08 p < .001	η^2 = .19	SCDclinic>HAS*** aMCI>HAS***
APOE ε4 carriers: n (%)	17 (24%)	4 (15%)	**25 (50%)**	Fisher's exact test, p=.002		HAS>aMCI** SCDclinic>aMCI**

For numerical variables, we indicated mean ± standard deviation [1st quartile, median, 3rd quartile]. Fisher's LSD test was used as a post hoc: * p<.05, ** p<.01, *** p<.001. For the sake of readability, patients values are bolded when different from the HAS group (p<0.05). Group comparisons were also assessed using Kruskal-Wallis and Mann-Whitney tests because some variables (recognition, depression) had strongly skewed distributions; results were unchanged. Percentages of APOE ε4 carriers are calculated based on the number of available genotypes within each group (n=72 for HAS, n=26 for SCDclinic, n=50 for aMCI).
FCSRT: Free and Cued Selective Reminding test; MADRS: Montgomery-Asberg depression rating scale; CDS: Cognitive Difficulties Scale. # indicates the scores that were used in the inclusion battery.

Table 2. List of the 39 items included in the Cognitive Difficulties Scale

Item order	factor 1	factor 2	factor 3
1. I have trouble recalling frequently used phone numbers	-0.037	**0.547**	-0.04
2. I put down things (glasses, keys, wallet, papers) and have trouble finding them	0.104	**0.473**	-0.056
3. When interrupted while reading, I have trouble finding my place again	**0.526**	0.176	-0.095
4. I need a written list when I do errands to avoid forgetting things.	0.09	**0.607**	-0.208
5. I forget appointments, dates or classes	-0.008	**0.679**	0.022
6. I forget to return phone calls	-0.055	**0.48**	0.281
7. I have trouble getting my keys into a lock	n/i	n/i	n/i
8. I forget errands I planned to do on my way	0.215	**0.474**	0.007
9. I have trouble recalling names of people I know	0.398	0.375	-0.121
10. I find it hard to keep my mind on a task or a job	**0.6**	-0.02	0.111
11. I have trouble describing a program I just watched on television	**0.69**	0.129	-0.152
12. I don't say quite what I mean	**0.475**	0.055	0.134
13. I fail to recognize people I know	0.393	0.037	0.145
14. I have trouble getting out information that's at the tip of my tongue.	**0.539**	0.017	-0.005
15. I have trouble finding the name of objects	**0.449**	-0.071	0.369
16. I find it hard to understand what I read	**0.758**	-0.335	0.204
17. I miss the point of what other people are saying	**0.573**	0.033	0.117
18. I forget names of people soon after being introduced	0.372	0.319	-0.014
19. I lose my train of thought when I listen to somebody else	**0.718**	0.272	-0.253
20. I forget steps in recipes I know well and have to look them up	0.182	0.108	**0.439**
21. I forget what day of the week it is	-0.082	**0.672**	0.102
22. I forget to button or zip my clothing	n/i	n/i	n/i
23. I need to check or double check whether I locked the door, turned off the stove, etc	0.009	**0.412**	0.147
24. I make mistakes in writing, typing or operating a calculator	0.168	0.143	0.322
25. I cannot keep my mind on one thing	**0.484**	-0.11	0.311
26. I need to have instructions repeated several times	0.129	**0.439**	0.192
27. I leave out ingredients when I cook	0.119	-0.031	**0.64**
28. I have trouble manipulating buttons, fasteners, scissors, or bottle caps	0.073	-0.105	**0.719**
29. I misplace my clothing	-0.046	0.049	**0.602**
30. I have trouble sewing or mending	-0.097	-0.084	**0.76**
31. I find it hard to keep my mind on what I'm reading	**0.667**	0.004	0.031
32. I forget right away what people say to me	**0.422**	**0.414**	-0.063
33. When walking or riding, I forget how I've gotten from one place to another.	n/i	n/i	n/i
34. I have trouble deciding if I have received the correct change	n/i	n/i	n/i
35. I forget to pay bills, record checks, or mail letters	-0.152	0.3	**0.491**
36. I have to do things very slowly to be sure I'm doing them right	0.017	0.251	**0.411**
37. My mind goes blank at times	0.194	**0.456**	0.047
38. I forget the date of the month	-0.283	**0.943**	0
39. I have trouble using tools (hammers, pliers, etc) for minor household repairs	-0.097	-0.013	**0.844**

The three columns on the right show the loading scores resulting from the exploratory factor analysis (see method section for further information). Factor loadings above 0.4 are bolded. 4 items were not included (n/i) in the factor analysis due to insufficient variability but were still included in item-by-item analyses

Figure 1. Item-by-item responses and group comparisons.

The top panel shows the distribution of responses for each item within each clinical group (an alternative version of the figure is available in ***Supplementary Figure 2*** and numerical data is available in ***Supplementary Table 2***). The top left box illustrates data presentation using diverging stacked bar plots, which enable precise visualization of the responses for each item within each group while showing global between-group trends (stronger endorsement in one group shifts the corresponding bar to the right). Note that the axis scale and increment were kept identical for all items to allow visual comparison. The full phrasing of all items is available in Table 2 but keywords are indicated in the present figure for the sake of simplicity.

Kruskall-Wallis test was first used to identify items that showed group differences: * indicates an uncorrected $p<0.05$ while ** highlights items surviving stringent Bonferroni correction ($p < 0.001282 = 0.05/39$). The two contrasts of interest were tested using Mann Whitney tests; bottom panel shows effect sizes ($r^2 = Z^2/n$) for each contrast (plain color for items surviving Bonferroni correction on the Kruskal-Wallis test, transparent color for others); # indicates significant group difference surviving Bonferroni correction for post hocs ($p < 0.025 = 0.05/2$).

Values are described in ***Supplementary Table 2*** and details of the statistical tests can be found in ***Supplementary Table 3***.

Figure 2. SCD factor scores across clinical groups.

After the group*Factor interaction was significant ($F(4, 364) = 11.33$, $p<.001$), between-group differences were assessed for each factor. Fisher's LSD was used as a post hoc test: *p<.05, ** p<.01, *** p<.001.

Scatter plot show individual values, as well as 10^{th}, 30^{th}, 50^{th}, 70^{th} and 90^{th} percentiles within each group (black lines). Values are described in ***Supplementary Table 4***.

Figure 3. Association between SCD and Aβ status in HAS and patients with aMCI.

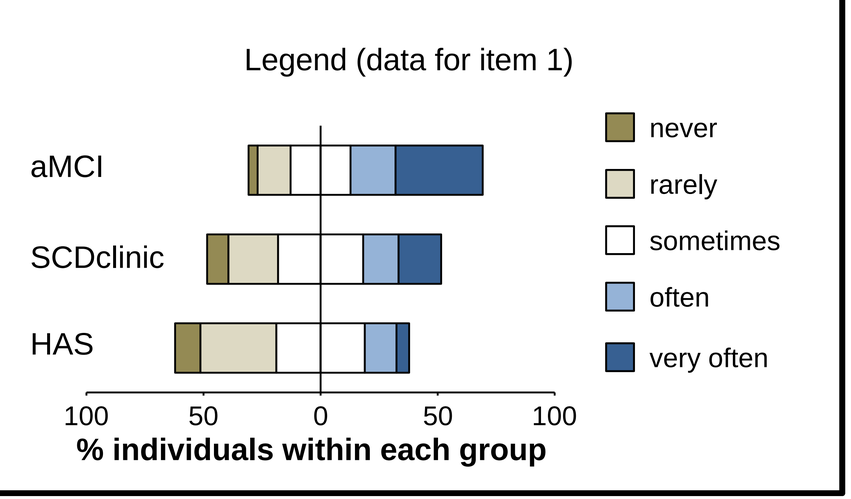
Left panel: item by item analyses. Mann-Whitney tests were used to compare individuals with and without evidence of Aβ using Florbetapir-PET. The figure illustrates the effect size ($r^2 = Z^2/n$) of the comparison. Filled bars indicate that the group difference reached an uncorrected threshold of $\alpha = 0.05$ (but none was significant when using Bonferroni procedure to correct for the 39 tests). Further description of item scores and statistical comparison is available in ***Supplementary Table 5*** (for HAS) and ***Supplementary Table 6*** (for patients with aMCI).

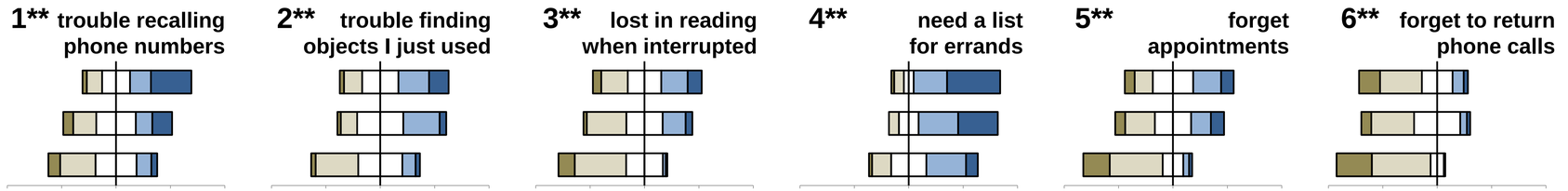
Right panel: Factor score analysis. After the (Clinical Group * Factor * Aβ Status) interaction was significant ($F(1, 114) = 9.00$, $p = .003$), a repeated model ANOVA was conducted within each clinical group. *p<.05, ** p<.01. Scatter plot show individual values, as well as 10^{th}, 30^{th}, 50^{th}, 70^{th} and 90^{th} percentiles within each group (black lines).

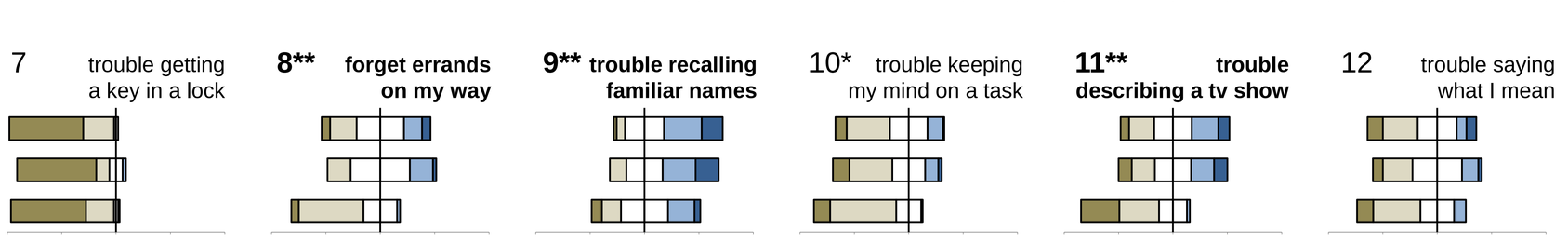
Figure 4. Association between SCD and cognitive scores.

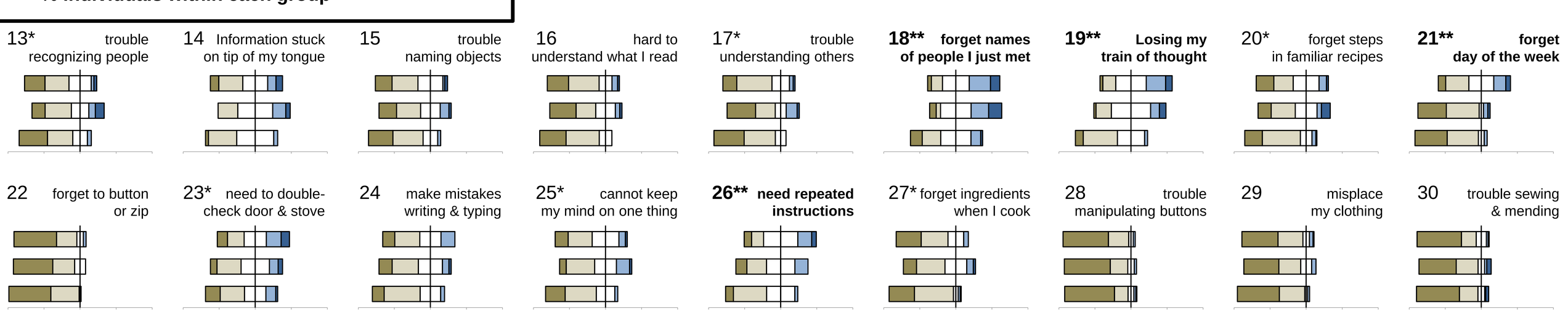
Left panel: item by item correlations between item endorsement and cognitive scores within each group (green: HAS, yellow: SCDclinic, red:aMCI). Correlations were assessed using non-parametric Spearman's coefficient; filled bars indicate that the correlation reached an uncorrected threshold of $\alpha = 0.05$ while # indicates items that survived stringent Bonferroni correction ($p < 0.001282 = 0.05/39$). Positive coefficients indicate that higher levels of self-reported cognitive difficulties are associated with better cognitive performances.

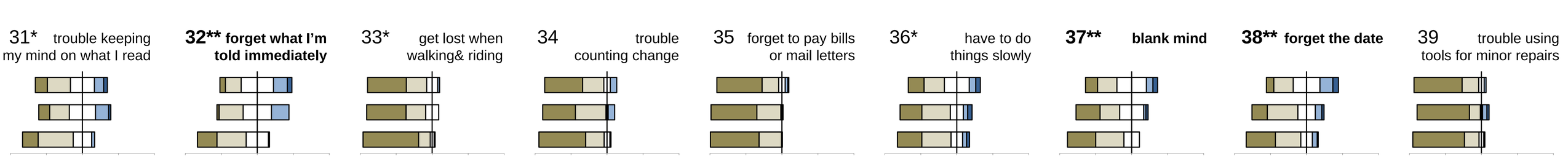
Right panel: correlation between SCD factor scores and cognitive scores within each group. Correlations were assessed using non-parametric Spearman's coefficient. Positive coefficients indicate that higher levels of self-reported cognitive difficulties are associated with better cognitive performances.

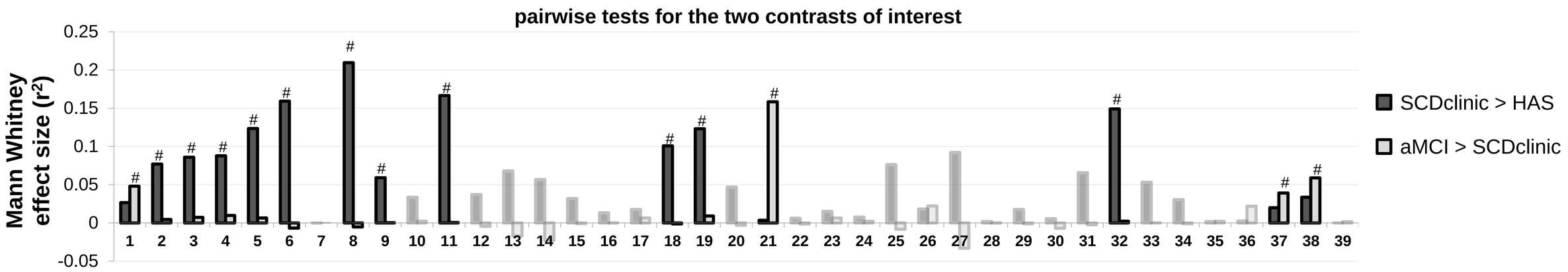

Legend (data for item 1)
aMCI
SCDclinic
HAS
never
rarely
sometimes
often
very often
100
50
0
50
100
% individuals within each group

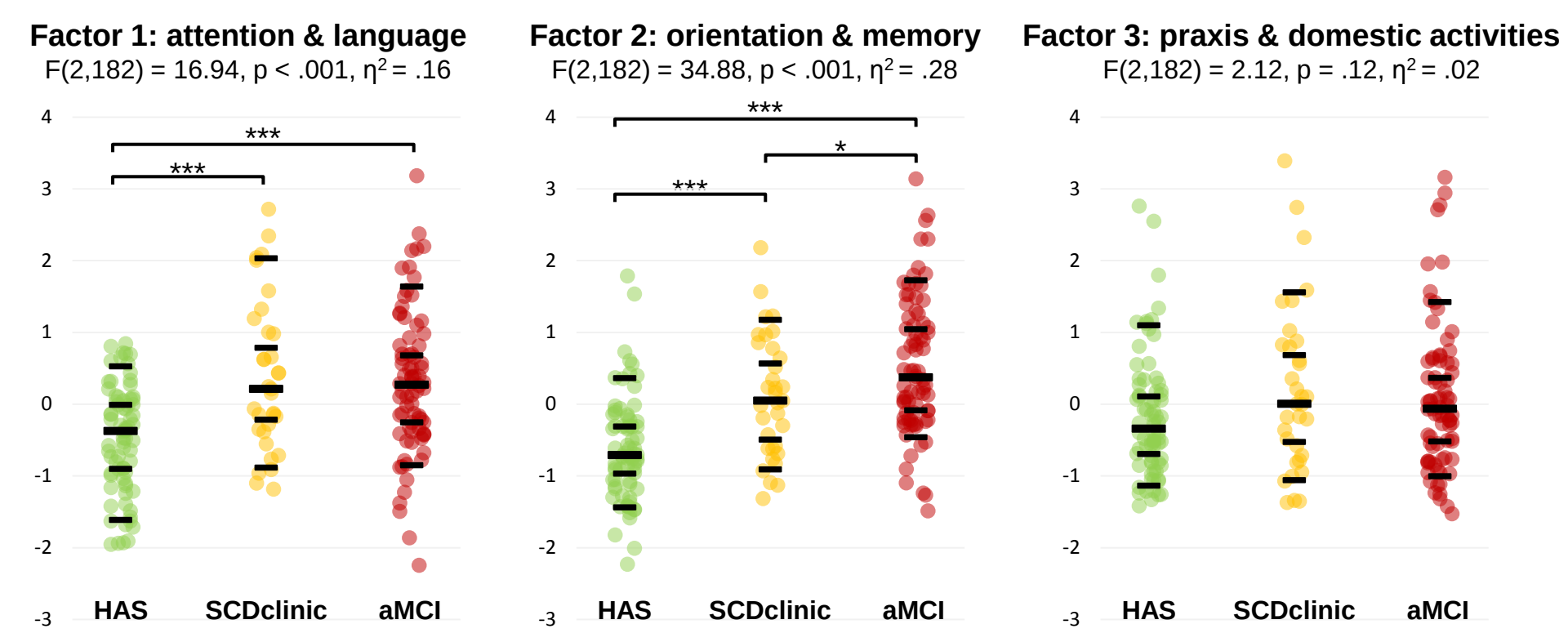

1** trouble recalling phone numbers
2** trouble finding objects I just used
3** lost in reading when interrupted
4** need a list for errands
5** forget appointments
6** forget to return phone calls

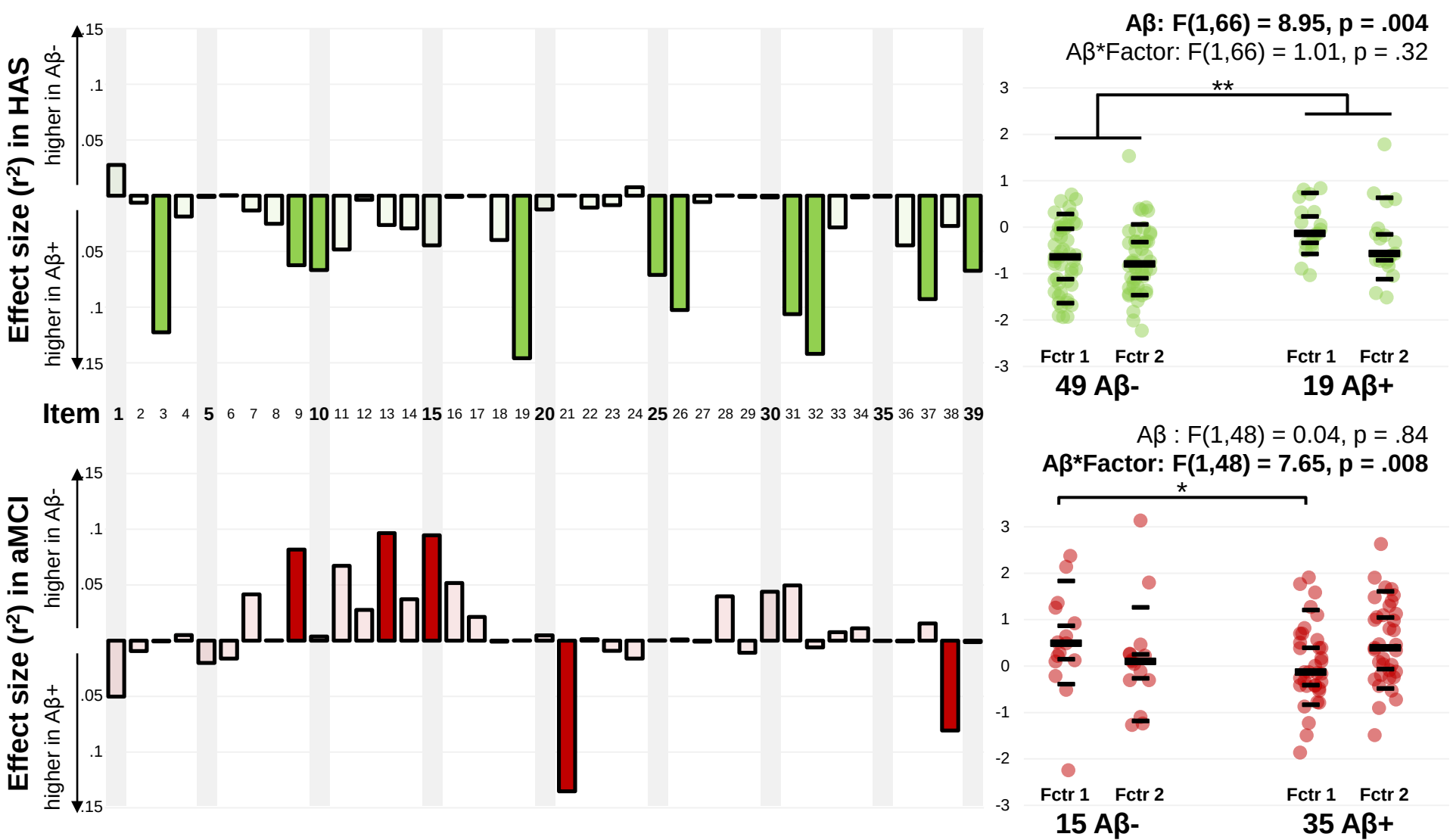

7 trouble getting a key in a lock
8** forget errands on my way
9** trouble recalling familiar names
10* trouble keeping my mind on a task
11** trouble describing a tv show
12 trouble saying what I mean

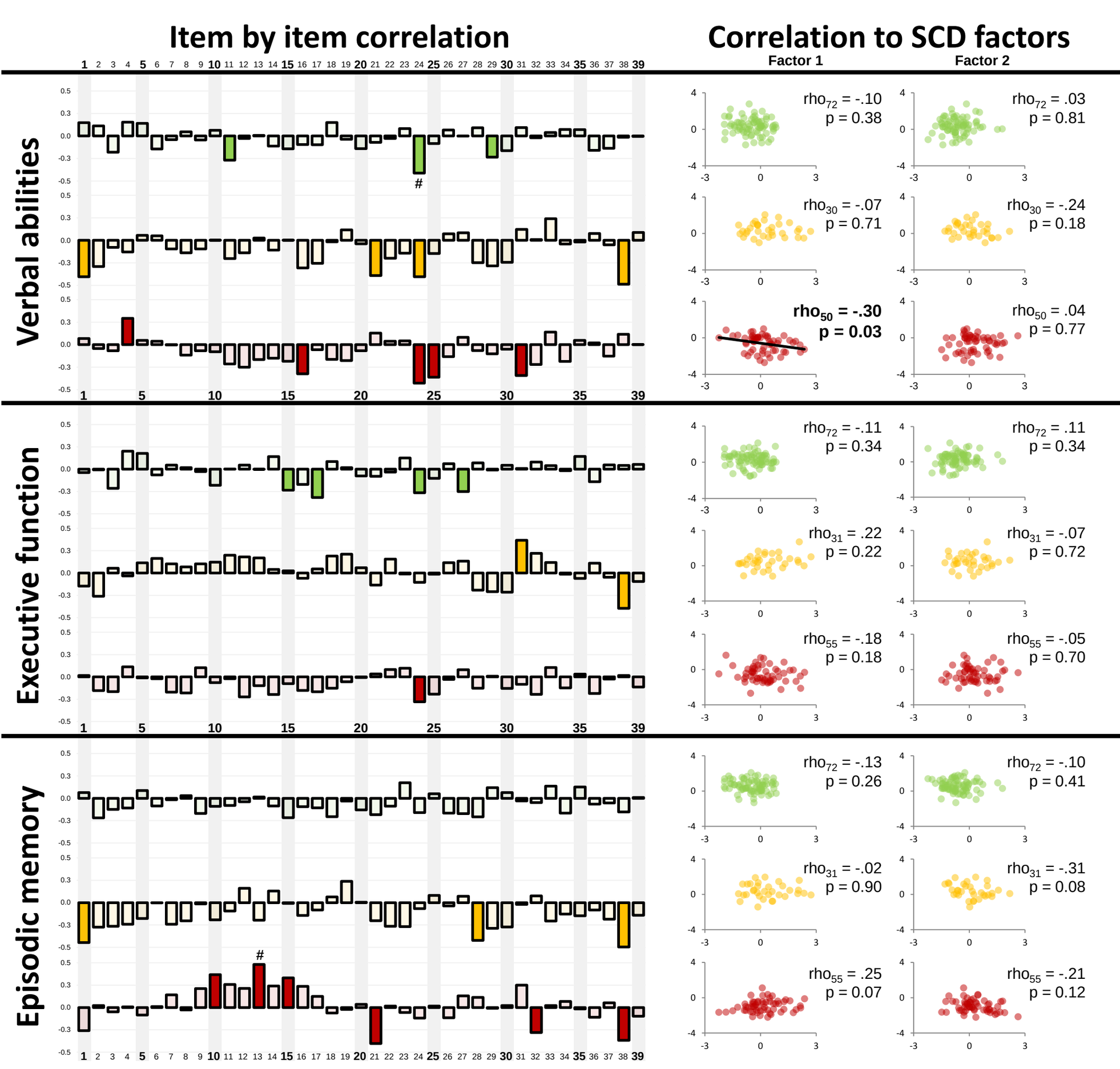

13* trouble recognizing people
14 Information stuck on tip of my tongue
15 trouble naming objects
16 hard to understand what I read
17* trouble understanding others
18** forget names of people I just met
19** Losing my train of thought
20* forget steps in familiar recipes
21** forget day of the week
22 forget to button or zip
23* need to double-check door & stove
24 make mistakes writing & typing
25* cannot keep my mind on one thing
26** need repeated instructions
27* forget ingredients when I cook
28 trouble manipulating buttons
29 misplace my clothing
30 trouble sewing & mending


31* trouble keeping my mind on what I read
32** forget what I'm told immediately
33* get lost when walking& riding
34 trouble counting change
35 forget to pay bills or mail letters
36* have to do things slowly
37** blank mind
38** forget the date
39 trouble using tools for minor repairs


pairwise tests for the two contrasts of interest
Mann Whitney effect size (r²)
0.25
0.2
0.15
0.1
0.05
0
-0.05
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39
SCDclinic > HAS
aMCI > SCDclinic


Factor 1: attention & language
F(2,182) = 16.94, p < .001, η² = .16
***
***
4
3
2
1
0
-1
-2
-3
HAS
SCDclinic
aMCI
Factor 2: orientation & memory
F(2,182) = 34.88, p < .001, η² = .28
***
*
***
4
3
2
1
0
-1
-2
-3
HAS
SCDclinic
aMCI
Factor 3: praxis & domestic activities
F(2,182) = 2.12, p = .12, η² = .02
4
3
2
1
0
-1
-2
-3
HAS
SCDclinic
aMCI


Effect size (r^2) in HAS
higher in Aβ-
higher in Aβ+
.15
.1
.05
Item 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39
Aβ: F(1,66) = 8.95, p = .004
Aβ*Factor: F(1,66) = 1.01, p = .32
**
Fctr 1
Fctr 2
49 Aβ-
19 Aβ+
Effect size (r^2) in aMCI
Aβ : F(1,48) = 0.04, p = .84
Aβ*Factor: F(1,48) = 7.65, p = .008
*
15 Aβ-
35 Aβ+


Item by item correlation
Correlation to SCD factors
Factor 1
Factor 2
Verbal abilities
Executive function
Episodic memory
#
rho72 = -.10
p = 0.38
rho72 = .03
p = 0.81
rho30 = -.07
p = 0.71
rho30 = -.24
p = 0.18
rho50 = -.30
p = 0.03
rho50 = .04
p = 0.77
rho72 = -.11
p = 0.34
rho72 = .11
p = 0.34
rho31 = .22
p = 0.22
rho31 = -.07
p = 0.72
rho55 = -.18
p = 0.18
rho55 = -.05
p = 0.70
rho72 = -.13
p = 0.26
rho72 = -.10
p = 0.41
rho31 = -.02
p = 0.90
rho31 = -.31
p = 0.08
rho55 = .25
p = 0.07
rho55 = -.21
p = 0.12