TESE DE DOUTORAMENTO

AFFECTIVE AND BEHAVIORAL SYMPTOMS IN THE AGE-RELATED COGNITIVE IMPAIRMENT CONTINUUM: ASSESSMENT AND PREDICTIVE VALIDITY

Sabela C. Mallo

ESCOLA DE DOUTORAMENTO INTERNACIONAL
PROGRAMA DE DOUTORAMENTO EN DESENVOLVEMENTO PSICOLÓXICO, APRENDIZAXE E SAÚDE

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Dña. Sabela C. Mallo López

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D. Arturo X. Pereiro Rozas

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DEDICATORIA

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ABSTRACT

Introduction: Affective and behavioral symptoms (ABS) correspond to those non-cognitive behavioral or psychiatric expressions that are indicative of an increased risk of dementia. Mild Behavioral Impairment (MBI) is a diagnostic entity proposed in order to describe the emergence of sustained and impactful ABS in pre-dementia states. The Neuropsychiatric Inventory (NPI) and the Neuropsychiatric Inventory - Questionnaire (NPI-Q) are the most common instruments to assess ABS. To overcome some caveats of these instruments, the Mild Behavioral Impairment - Checklist (MBI-C) was developed.

Methods: To review and analyze ABS as risk factors for conversion to dementia a meta-analysis was conducted. Longitudinal studies were included when concerned with the role of ABS as risk factors for conversion from MCI to dementia and reported NPI/NPI-Q total score in converters versus non-converters. Random effects models were used, and heterogeneity was explored with stratification and a random-effects meta-regression. The overall conversion rate and the Standardized Mean Difference (SMD) for evolution, as a function of NPI/NPI-Q scores, were calculated. The other three studies included in this thesis come from the first cohort of the Compostela Aging Study, carried out in primary care centers. Patients with SCD and MCI were recruited at baseline. They performed an extensive neurocognitive evaluation. Two studies examined the prevalence and some psychometric properties of the MBI-C in a sample of, respectively, participants with SCD and MCI. We conducted descriptive, logistic regression, ROC curve, and bivariate correlations analyses. A Machine Learning (ML) study was conducted to determine if NPI-Q scores predict conversion from MCI to dementia. Nine ML algorithms were evaluated using a 10-fold stratified validation procedure. Performance metrics, graphic metrics and features analysis were computed.

Results: In the meta-analysis, mean NPI/NPI-Q scores were higher in converters versus in non-converters, with the overall SMD approaching significance. Statistical significance was achieved in studies of more than two years of follow-up and in a study with a mean age of more than 80 years. MBI diagnosis prevalence was 14.2% in MCI and 5.8% in SCD. The total MBI-C score successfully differentiated patients with MBI at a cut-off of 6.5 in MCI and 8.5 in SCD. MBI-C total score correlated positively with the NPI-Q, Questionnaire for Subjective Cognitive Complaints reported by the informant, and Geriatric Depression Scale in the SCD and MCI samples. In the ML study, the algorithm indicated the predictive importance of the following measures: months from first assessment, age, the diagnostic group at baseline, total NPI-Q severity score, total NPI-Q stress score, and GDS-15 total score.

Conclusions: NPI/NPI-Q total score was associated with conversion from MCI to dementia, particularly in studies with two or more years of follow-up and a mean age of over 80 years. The phone administration of the MBI-C was valid for detecting MBI in people with SCD and MCI. ABS proxies, including NPI-Q total severity score, NPI-Q total stress score, and GDS-15 total score, were the more relevant variables in predicting conversion from MCI to dementia.

Keywords: Affective and Behavioral Symptoms, predictive validity, Mild Behavioral Impairment- Checklist, Neuropsychiatric-Inventory, pre-dementia states.

EXTENDED ABSTRACT IN GALICIAN LANGUAGE

SÍNTOMAS AFECTIVOS E CONDUCTUAIS NO CONTINUO DO DETEREIORO COGNITIVO RELACIONADO COA IDADE: AVALIACIÓN E CAPACIDADE PREDICTIVA

RESUMO EXTENDIDO

Introdución: O deterioro normativo ligado á idade ás veces acontece xunto con procesos neurodexenerativos. Nestas circunstancias, o progresivo deterioro cognitivo asociado á idade pódese representar nun continuo que vai dende o envellecemento normal á demencia (Jack et al., 2018). Nel pódense diferenciar varios estadios: de cognición obxectivamente inalterada en relación ao seu grupo de referencia por idade e nivel educativo, Deterioro Cognitivo Subxectivo (DCS), Deterioro Cognitivo Lixeiro (DCL) e demencia.

O Deterioro Cognitivo Subxectivo (DCS) caracterízase por unha experiencia subxectiva de declive cognitivo persistente e significativa en comparación cun nivel previo, que non ten relación cun evento concreto, e cun rendemento cognitivo dentro da media para a súa idade e nivel educativo (Jessen et al., 2014, 2020). As queixas cognitivas son a características fundamental das persoas con DCS, e asócianse con deterioro cognitivo e progresión a DCL e demencia (Burmester, Leathem & Merrick, 2016; Jessen et al., 2011; Masters, Morris, & Roe, 2015a).

O Deterioro Cognitivo Lixeiro (DCL) considérase unha entidade diagnostica caracterizada por queixas cognitivas informadas pola propia persoa, un informante ou un profesional, e sobre todo por un deterioro obxectivo nun ou varios dominios cognitivos por debaixo do esperado para a súa idade e nivel educativo, conservar a independencia para as habilidades da vida diaria e ausencia de demencia (Albert et al., 2011).

Na demencia prodúcese un declive acentuado nun ou máis dominios cognitivos, que se reflicte na preocupación por parte da propia persoa, dun familiar ou dun profesional, e un deterioro substancial na súa funcionalidade (American Psychiatric Association [APA], 2013). A Enfermidade de Alzheimer (EA) e o tipo de demencia máis prevalente (Alzheimer's Association [AA], 2016).

Entre os factores de risco de demencia e EA atópanse os Síntomas Afectivos e Conductuais (SAC), tamén denominados Síntomas Neuropsiquiátricos (Neuropsychiatric Symptoms - NPS) (Connors, Ames, Woodward, & Brodaty, 2017; David, Lin, Porsteinsson, & Alzheimers Disease Neuroimaging Initiative [ADNI], 2016; Geda et al., 2014). Estes son síntomas condutuais non-cognitivos entre os que se inclúen perturbacións do estado de ánimo, percepción e comportamento relacionados cun trastorno neurocognitivo (Lyketsos et al., 2011). Recentemente, unha área de interese profesional (Proffesional Interest Area - PIA) da Sociedade Internacional para o Avance na Investigación e Tratamento do Alzheimer (International Society to Advance Alzheimer Research and Treatment - ISTAART) identificou o inicio de SAC prolongados ó longo do tempo nos últimos anos da vida cun maior risco de declive cognitivo e demencia (Ismail et al., 2016; Ismail et al., 2017a). Os SAC asócianse con maior risco de deterioro cognitivo e demencia (Connors et al., 2017; David et al., 2016; Geda et al., 2014).

O Deterioro Comportamental Leve (DCoL) é unha entidade diagnóstica validada que describe a aparición de ABS sostidos e impactantes nos estados pre-demencia e considérase un

estado de risco para o deterioro cognitivo e a demencia (Ismail et al., 2016). Os criterios especifican que os síntomas deben implicar un cambio significativo na personalidade ou conducta previa da persoa. Ademais os síntomas deben estar presentes polo menos durante 6 meses. Os síntomas agrúpanse en cinco dominios: diminución da motivación, desregulación afectiva, descontrol dos impulsos, conducta social inapropiada e percepción ou contido do pensamento anormal. Os comportamentos deben presentar a suficiente severidade como para provocar sutís interferencias nas relaciones sociais, capacidade para traballar ou outros aspectos do funcionamento social, aínda que mantendo a independencia para a vida diaria, con axudas mínimas. Ademais, non deben cumprirse criterios de demencia (aínda que pode diagnosticarse DCL de forma comórbida) nin os síntomas deben poder asociarse a outro trastorno.

O Inventario Neuropsiquiátrico (Nueropsichiatric Inventory - NPI) e a súa versión abreviada, o Inventario Neuropsiquiátrico - Cuestionario (Nueropsichiatric Inventory-Questionnarie - NPI-Q), son os instrumentos máis comúns na valoración dos SAC (Ismail e Mortby, 2017).

O NPI é unha entrevista informada estruturada (Cummings et al., 1994) que proporciona unha forma de avaliación subxectiva que realiza o coidador sobre a presenza, frecuencia e gravidade de 12 síntomas (delirios, alucinacións, axitación / agresión, disforia / depresión, ansiedade, irritabilidade, desinhibición, euforia, apatía, comportamento motor aberrante, comportamento durante o sono e pesadelos e apetito / cambios na alimentación). O coidador tamén informa do nivel de estrés que padece sobre ese SAC. No NPI-Q, pola contra o coidador segue instrucións escritas para completar o cuestionario (Kaufer et al., 2000).

Tanto o NPI como NPI-Q, así como a maioría das escalas tradicionais, foron creadas para poboación clínica con demencia, empregando como marxe temporal dúas ou catro semanas. O MBI-C (Ismail et al., 2017a) é unha escala recente que foi deseñada especificamente para o DCoL baseándose nos criterios ISTAART-AA e foi adaptado ao castelán por Agüera-Ortiz e López-Álvarez (2017). Foi creada para unha poboación comunitaria, independente e funcional. O instrumento solicita que os síntomas aparezan nos últimos anos da vida e se manteñan durante polo menos seis meses. Inclúe 34 ítems agrupados nos cinco dominios aos que fai referencia o DCoL. É un instrumento breve que pode ser cuberto polo propio paciente, un informante ou un clínico.

Método: Esta tese está conformada por catro artigos de investigación. No primeiro deles, propúxenme revisar e metaanalizar a capacidade dos SAC, medidos co NPI / NPI-Q, para predicir a progresión desde o DCL ata a demencia. Nesta metaanalise incluíronse artigos publicados entre xaneiro de 1999 e setembro de 2018 en PsycINFO, PubMed, SCOPUS e Web of Science. Os criterios de inclusión foron: 1) diagnóstico de DCL en liña base seguindo criterios clínicos; 2) informar da puntuación total do NPI ou NPI-Q en persoas que converten e que non converten a demencia; 3) estudos empíricos lonxitudinais; e 4) centrados no papel dos SAC como factores de risco para a conversión de DCL a demencia. Os criterios de exclusión establecéronse para artigos que: a) se realizaran con mostras que contiñan a maioría de participantes dunha poboación especial (por exemplo: pacientes con cancro); e b) careceran de información importante e non fora posible contactar cos autores para completala. Utilizáronse modelos con efectos aleatorios e explorouse a heteroxeneidade con estratificación e unha meta-regresión con efecto aleatorio. Calculouse a taxa de conversión global e a diferenza de media estandarizada (Standarized Mean Difference - SMD) para a evolución, en función das puntuacións NPI / NPI-Q.

Os outros tres estudos desta tese proceden da primeira cohorte do estudo lonxitudinal 'Compostela Ageing Study' (CompAS), realizado con participantes de 50 ou máis anos de idade con queixas subxectivas recrutados en centros de atención primaria. Foron excluídos do estudo: 1) participantes con diagnóstico previo de depresión ou outros trastornos psiquiátricos seguindo os criterios DSM-5 (APA, 2013); 2) con diagnóstico previo de enfermidade neurolóxica, incluída EA probable ou outros tipos de demencia segundo os criterios DSM-5 (APA, 2013); 3) con danos cerebrais previos ou cirurxía cerebral; 4) sometidos a quimioterapia; 5) con diagnóstico previo de diabetes tipo II; 6) con perturbacións sensoriais ou motoras; e 7) que consumen substancias que poden afectar ao desempeño nas probas.

Os participantes sometéronse a unha avaliación cognitiva, afectivo-condutual e clínica, incluíndo un cuestionario sociodemográfico, o índice de Comorbilidade de Charlson (ICC) (Charlson et al., 1987) e unha breve versión española do cuestionario para queixas subxectivas de memoria (QSMC) (Benedet e Seisdedos, 1996). O rendemento cognitivo xeral avaliouse coa versión española (Lobo et al., 1999) do Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) e a versión española (López-Pousa, 2003; Pereiro, Ramos-Lema, Juncos-Rabadán, Facal & Lojo-Seoane, 2015) do Cambridge Cognitive Examination-Revised (CAMCOG-R) (Roth, Tym, & Mountjoy, 1986). O índice Lawton and Brody utilizouse para avaliar as actividades instrumentais da vida diaria (Lawton e Brody, 1969).

Os SAC avaliáronse coa versión española do NPI-Q (Boada, Cejudo, Tàrraga, López, & Kaufer, 2002) e coa versión española do GDS-15 (Martínez et al., 2001). Tamén se empregou a versión española do MBI-C (Agüera-Ortiz e López-Álvarez, 2017).

O DCS diagnosticouse seguindo os criterios de Jessen et al. (2014), e o DCL seguindo os de Albert et al. (2011). O DCoL diagnosticous de acordo ós criterios ISTAART-AA (Ismail et al., 2016).

Realizáronse dous artigos, co obxectivo de estudar a prevalencia do DCoL e algunhas propiedades psicométricas do MBI-C administrado por teléfono aos informantes e determinar se este instrumento é válido para valorar os SAC, respectivamente, nos participantes con DCS e con DCL. Neles, realizaronse análises descritivas, de regresión loxística, calculo de curva ROC e de correlacións bivariadas.

Para determinar se as puntuacións no NPI-Q predín a conversión a demencia en participantes con DCS e DCL empregáronse técnicas de Machine Learning (ML) e o resultados deron lugar a un cuarto artigo. Avaliáronse nove algoritmos mediante un procedemento de validación estratificada por 10 veces. Para cada algoritmo se computaron métricas de rendemento (precisión, recordo, puntuación F-1 e kappa de Cohen) e representáronse a través da curva ROC e curva de precisión-recordo. A maiores, analizáronse as características dos algoritmos que presentaban un mellor rendemento preditivo. As variables predictivas incluídas foron: diagnóstico en liña base, meses desde a avaliación en liña base ata o terceiro seguimento ou desenvolvemento de demencia, xénero, idade, ICC, ítems individuais do NPI-Q, gravidade total NPI-Q, puntuación de estrés total do NPI-Q e puntuación total na GDS-15. A parte dos análises de ML, tamén se realizaron comparacións entre persoas que converten e as que non converten a través do test U de Mann-Witney.

Resultados: No que se refire á metaanálise, o análise da SMD (d de Cohen) amosou unha heteroxeneidade estatisticamente significativa (I^2 =70%, χ^2 = 33.33, p<0.001, τ^2 = 0.082). O funnel plot non indicou sesgos de publicación, e os tests de Egger (t = -0.18, p = 0.865) e Begg (z=1.25, p= 0.213, continuidade corrixida) non foron significativos. O valor da SMD agrupada

foi de 0.21, indicando un tamaño do efecto pequeno que se aproximou a significación no modelo de efectos aleatorios (z=1.95, p= 0.052).

Con respecto do conxunto de sete estudos con máis de dous anos de seguimento, (I^2 = 76.1 %, χ^2 =, 25.16, p<0.001, τ^2= 0.12), a SMD (0.34, 95 % CI 0.04-0.63) alcanzou un valor significativo (z=2.23, p=0.026).

Eliminando o estudo de Bidzan, Bidzan, & Bidzan-Bluma (2017) suprimiuse a heteroxeneidade (I^2 = 0 and τ^2 = 0), de maneira que o modelo de efectos aleatorios se aproximaba a un modelo de efectos fixos, a SMD foi de 0.171 (95% CI 0.027 – 0.314) e continuou sendo significativa (z = 2.33, p= 0.020).

Estratificando a meta-análise en base os estudos que teñen participantes de 80 anos ou máis na súa mostra ou 80 anos ou menos, os resultados indicaron que a SMD non era significativa en 10 estudos cunha media de idade menor de 80 (SMD = 0.20, 95 % CI -0.05-0.45, z = 1.54, p = 0.124). A estratificación en base a outras variables non explicou a heteroxeneidade.

En canto aos artigos de prevalencia do DCoL e análise das propiedades psicométricas do MBI-C, en persoas con DCS a prevalencia do DCoL foi de 5.8% e no DCL de 14.2%. En persoas con DCS a puntuación total no MBI-C foi moi baixa, co 76.5% da mostra puntuando cero e 9.6% puntuando un. En persoas con DCL a puntuación total do MBI-C foi baixa, co 23.6% puntuando cero e 11.3% puntuando un.

Tanto en DCS como en DCL a puntuación total do MBI-C correlacionou positiva e significativamente co NPI-Q (DCS: ρ= 0.57; p<0.01; DCL: ρ= 0.62; p< 0.01), QSMC do informante (DCS: ρ= 0.30 p< 0.01;DCL: ρ=0.46; p< 0.01) e GDS-15 (DCS: ρ=0.22 p< 0.05; DCL: ρ=0.23;p<0.05). O Índice de Lawton e Brody asociouse negativamente e significativamente co MBI-C en persoas con DCL (ρ= –0.26; p<0.05), pero en DCS esta asociación non foi significativa. Tampouco se encontraron relacións significativas co MMSE, o CAMCOG, nin co QSMC do paciente en DCL nin en DCS.

A regresión loxística indicou que o MBI-C é un predictor significativo do diagnóstico de DCoL en persoas con DCS (β= −1.08; ST. E = 0.50; *Wald*=4.63; df=1, p < 0.05; OR = 0.34 CI (95%) = 0.12–0.90) e DCL (β = –0.48; ST.E = 0.13; *Wald* = 14.22; df=1, p < 0.0001; OR = 0.62 CI (95%) = 0.48–0.79) . A R^2 de Nagelkerke indicou que o modelo explica o 85% da varianza para DCS e o 64% para DCL. O Test de Hosmer–Lemeshow indicou un bo axuste para o modelo de regresión para DCS (χ^2 =2.50, df = 4, p = 0.99) e DCL (χ^2 = 10.71, df=8, p = 0.22). A curva ROC indicou que as puntuacións totais no MBI-C diferenciaba con precisión a persoas con diagnóstico de DCoL tanto en DCS como en DCL. O punto de corte para DCS estableceuse en 8.5 con boa sensibilidade = 1.0 (95% CI: 1.0–1.0), especificidade = 0.96 (95% CI 0.92–0.99) e área baixo a curva = 0.99, p < 0.001 (95% CI: 0.98–1.0). Para DCL, o punto de corte estableceuse en 6.5, alcanzando valores de sensibilidade = 1.00, especificidade = 0.78 e área baixo a curva= 0.93, p < 0.001.

No cuarto e último artigo, a análise U de Mann-Whitney permitiu observar diferenzas significativas entre as persoas que converten fronte ás que non en relación á idade, severidade total do NPI-Q, estrés total do NPI-Q, alucinacións, agresións, axitación, ansiedade, apatía, desinhibición, irritabilidade, conducta motor aberrante e trastornos alimentarios. As persoas que converteron eran máis maiores e as súas puntuacións para estes SAC foron máis elevadas que nas persoas que non convertían a demencia. Non se atoparon diferenzas significativas na comorbilidade, puntuación total da GDS-15, delirios, depresión / disforia, euforia ou alteracións do sono.

En canto as análises de ML, o algoritmo Random Forest Plot estableceu como variables máis importantes na predición: meses desde a primeira avaliación, idade, o grupo de diagnóstico na base, puntuación total de severidade no NPI-Q, puntuación total de estrés no NPI-Q e puntuación total na GDS-15.

Discusión: Os resultados da metaanalise suxiren que as puntuacións totais no NPI/NPI-Q predín significativamente a conversión a demencia en estudos lonxitudinais de máis de 2 anos de duración e con mostras de persoas con idades avanzadas. Varios estudos concluíron que os SAC aumenta o risco de demencia (Connors et al. , 2017; David et al., 2016; Geda et al., 2014). Os nosos resultados están aliñados cos destas investigacións, os tamaños do efecto estimados en todos os subgrupos foron na dirección de maiores puntuacións no NPI / NPI-Q en persoas que converten fronte ás que non, e a heteroxeneidade observada concernía o tamaño, non a dirección, da diferenza. Dado que o NPI e o NPI-Q son específicos para a demencia (Ismail et al., 2017a) os nosos resultados poden estar relacionados coa falta de sensibilidade ante os SAC que aparecen de forma máis temperán e a falta de especificidade ante os síntomas transitorios.

Os estudos cunha duración de máis de dous anos tiveron unha taxa de conversión maior que os que tiveron menos de dous anos de seguimento, coincidindo con investigacións previas (Cui et al., 2011; Facal, Guàrdia-Olmos, & Juncos-Rabadán, 2015). Deste xeito, os nosos resultados suxiren que o tempo pode que non sexa só unha variable chave na progresión dos síntomas cognitivos (Cui et al., 2011; Facal et al., 2015) senon tamén dos SAC.

Ademais, o efecto dos SAC na conversión parece ser maior nos estudos con participantes moi maiores. Investigacións anteriores expuxeron que a idade é unha variable de risco ao prever a evolución desde o DCL ata a demencia (Matthews, Stephan, Mckeith, & Bond, 2008).

No que se refire ós artigos de prevalencia do DCoL e análise das propiedades psicométricas do MBI-C, os resultados atopados suxiren que a aplicación telefónica do MBI-C a un informante é útil para detectar DCoL tanto en DCS como en DCL. O MBI-C foi un preditor significativo do diagnóstico de DCoL en DCS e DCL.

Estimouse unha prevalencia de 5.8% para DCS e de 14.2 para DCL. Estudos previos estimaron unha prevalencia moito máis elevada, de 43.1% para DCS e 48.9 para DCL nunha mostra poboacional (Mortby et al., 2018c), e de 76.5% para DCS e 85.3 nunha mostra clínica (Sheikh et al., 2018). Sen embargo, empregaron o NPI e o NPI-Q, que utiliza un período temporal de un mes, mentres que o MBI-C solicita que os síntomas estean presentes durante polo menos seis meses e aparezan durante os últimos meses de vida (Ismail et al., 2017a). Ademais no noso estudo empregamos todos os criterios da ISTAART-AA para realizar o diagnóstico de DCoL.

O MBI-C correlacionou significativa e positivamente co NPI-Q e a GDS-15, indicando boa validez converxente, tanto en DCS como en DCL.

Atopouse unha relación significativa entre o MBI-C e o Índice Lawton en Brody só en persoas con DCL, en DCS a relación non foi significativa. É importante destacar que o MBI establece que os SAC deben producir deterioro nas relación interpersoais, no rendemento no traballo ou noutros aspectos do funcionamento social (Ismail et al., 2016). As persoas con DCL, malia manter a súa funcionalidade para actividades instrumentais da vida diaria, poden empezar a amosar algún problema no desempeño tarefas funcionais complexas (Albert et al., 2011), a diferencia das persoas con SCD que non presentan problema algún de funcionalidade (Jessen et al., 2014). No MBI este deterioro funcional debe vir derivado de problemas de conducta, e non ser consecuencia dun posible deterioro cognitivo (Ismail et al., 2016).

Non se atopou correlación entre o MBI-C e o rendemento cognitivo (MMSE e CAMCOG) nin en DCS nin en DCL, o que suxire que, aínda que o MBI e o deterioro cognitivo poden ocorrer de forma simultánea, reflicten diferentes síndromes en fases pre-demencia (neuroconductual e neurocognitivo) (Ismail et al., 2016).

Tanto en DCS como en DCL, as queixas subxectivas do informante correlacionaron significativa e positivamente co MBI-C, a diferencia das observadas no propio doente. Juncos-Rabadán et al. (2012) suxiren que estes resultados poden ter que ver co maior valor preditivo das queixas informadas polos familiares con respecto das realizadas polo propios doentes.

Por último, no artigo de ML, os resultados indicaron que as persoas que converteron tiñan puntuacións máis elevadas no total de severidade NPI-Q fronte ás que non converteron, de acordo con estudos previos (Acosta, Borges, Aguirre-Hernandez, Sosa, & Prince, 2018; Forrester, Gallo, Smith, & Leoutsakos, 2016; Mortby, Burns, Eramudugolla, Ismail, & Anstey, 2017; Rosenberg et al., 2013). Ademais nos análises de ML o total de severidade do NPI-Q foi unha das principais variables predicindo conversión a demencia. Estudos anteriores indican que esta puntuación predí progresión de DCL á demencia (Banks et al., 2014; Mortby et al., 2017), mentres que outros non encontraron esta relación (Brodaty et al., 2011). É importante destacar que o NPI-Q é instrumento creado para pacientes con demencia, non para persoas con DCL, o que pode limitar a súa sensibilidade.

De acordo con estudos previos (Corrada, Brookmeyer, Paganini-hill, Berlau, & Kawas, 2010; Facal et al., 2015), a taxa de conversión incrementouse co tempo de seguimento e a idade dos participantes.

A GDS-15 tamén tivo un papel esencial predicindo a conversión de DCL a demencia. A depresión é o síntoma máis común no DCL (Ismail et al., 2017b). A GDS-15 foi máis predictiva de progresión que o ítem individual de depresión / disforia do NPI-Q. Este ítem individual é unha única pregunta acerca de se o paciente está triste, baixo de ánimo ou chora a miúdo (Kaufer et al., 2000) mentres que a GDS-15 é un test de 15 preguntas (Sheikh e Yesavage, 1986). A GDS-15 proporciona información moito máis extensa. Ademais, a GDS é unha medida autoinformada, mentres que o NPI-Q é cuberto polo informante. Polo tanto a información pode ser cualitativa e significativamente distinta (Sanchez-Villegas et al., 2008).

As conclusión principais ás que nos permiten chegar os estudos que compoñen esta tese doutoral son as seguintes:

1) A puntuación total do NPI/NPI-Q predí a conversión de MCI a demencia cun tamaño do efecto pequeno. A capacidade preditiva tórnase significativa en estudos lonxitudinais con mais de 2 anos de duración e en participantes cunha idade media de 80 ou máis anos.

2) A administración telefónica do MBI-C resultou válida na detección do MBI en participantes con DCS e DCL.

3) A prevalencia do MBI en participantes galegos recrutados en centros de atención primaria con DCL e DCS foi, respectivamente, baixa (14.8%) e moi baixa (5.2%).

4) Considerando as variables sociodemográficas, de saúde e que avalían os SAC na predición da conversión de DCL a demencia, as puntuacións totais de severidade e de estrés do NPI-Q e a puntuación total do GDS-15 foron as máis relevantes.

Palabras chave: Síntomas Afectivos e Conductuais, validez predictiva, Mild Behavioral Impairment- Checklist, Neuropsychiatric Inventory- Questionnaire, estadios pre-demencia.

1. INTRODUCTION

Dementia and cognitive impairment in older adults are leading contributors to disability and constitute a pressing and global public health priority. The number of people affected by this disease worldwide in 2015 was estimated at 47 million people (Prince, Guerchet & Prina, 2015) and some studies projected to triple in 2050 (Prince, Guerchet, Prina & Alzheimer's Disease International, 2013). In Spain, the number of people with this neurocognitive disorder in 2010 was estimated over 600,000 (Gustavsson et al., 2011). Galicia, is the second region of Spain with the highest percentage of older adults (Abellán-García, Vilches-Fuentes & Pujol-Rodríguez et al., 2014) and the number of people older than 64 years affected by dementia was estimated in 96.234 (Hermida-Porto, 2012). The most common type of dementia is Alzheimer's Disease (AD) (AA, 2016).

Currently, there are no disease-modifying therapies for dementia (Cummings, Ritter, & Zhong, 2018). AD clinical trial drugs have failed to meet their primary outcome measures (Messner et al., 2019). One of the many hypotheses to explain these discouraging results was that disease-modifying therapies must be administered earlier in the dementia course (Messner et al., 2019; Mortby et al., 2018a). Despite even currently the criterion of objective cognitive impairment is mandatory for the illness detection, some findings have suggested that this model may be imprecise and too late in the course of illness to allow a significant disease modification, at least for some of these patients (Gauthier et al., 2016; Mortby et al., 2018a). It has been suggested that earlier detection, using appropriate screening tools and complementary symptoms identification, could improve the accuracy of the individual's risk profile (Kivipelto, Mangialasche, Ngando 2018).

Hence, it is necessary to improve the early identification of dementia markers and their translation into useful tools (Mortby et al., 2018a; Mortby, Lyketsos, Geda & Ismail, 2018b). In this context, quickly and inexpensively procedures for identifying reliable markers of AD in the general population, and whose cognitive correlations could be measured over the short term, would be desirable (Creese et al., 2019a).

It has been suggested that the cognocentric model may not be enough to understand the symptomatic variety of the disease. Instead, a systematic approach using Affective and Behavioral Symptoms (ABS) of dementia, also frequently denominated Neuropsychiatric Symptoms (NPS), may improve the clinical trial design (Mortby et al., 2018a). The emergence of ABS may increase the risk of cognitive impairment, being a clinical feature to capture early phase illness (Geda et al., 2014). Historically, some ABS have been exclusion criteria for dementia clinical trials, but this may change if the evidence supports the predictive utility of these symptoms for cognitive decline in pre-dementia populations. A deeper understanding of how ABS influences the cognitive status of older adults is necessary. ABS could improve early case detection of elderly patients at risk of cognitive impairment and promote prevention (Mortby et al., 2018b). The inclusion of ABS could be considered for clinical trial methodology (Messner et al., 2019; Mortby et al., 2018a). For this purpose, it is fundamental to use appropriate instruments, adapted to the characteristics of the population that is being studied (Ismail et al., 2017a).

This dissertation aims to review and analyze the predictive relationship of the ABS in individuals with Subjective Cognitive Decline (SCD) and Mild Cognitive Impairment (MCI), to

study some psychometric properties of a checklist for the assessment of the ABS, and to examine the prevalence of ABS in these participants.

The introduction of the present work starts with an explanation of the continuum of age-related cognitive decline, including SCD and the diagnostic entities of MCI and dementia due to AD. A subsection is dedicated to AD progression and early detection, given the relevance of the identification of risk factors. The following section of the introduction is focused on ABS. After establishing the concept of ABS, Mild Behavioral Impairment (MBI) nosological entity is defined. Subsequently, different instruments to assess ABS are explained. Lastly, the role of ABS as predictors of conversion to dementia in people with SCD and MCI is reviewed.

1.1. The Continuum In Age-Related Cognitive Impairment

With increasing age, changes occur at the cognitive level (Lindenberger, 2014; Park & Schwarz, 2012). Crystallized abilities remain conserved or even experience an improvement. These skills refer to the accumulation of knowledge about the world (e.g., vocabulary and domain-specific knowledge). By contrast, fluid cognitive abilities (e.g., reasoning, working memory, attention, and executive control) experience a steady decline. These skills are less supported by acquired knowledge but help acquire that knowledge in the first place. Thus, cognitively unimpaired older adults are characterized by normal cognitive performance according to that expected for the age and education reference group.

In some cases, this normative decline may also progress in association with neurodegenerative processes. This progressive cognitive impairment can be represented in a continuum from normative aging to dementia (Jack et al., 2018; Petersen et al., 2018). Different stages along the continuum were explicitly considered by the National Institute on Aging-Alzheimer's Association (NIA-AA) in 2018 (Jack et al., 2018) and included SCD, MCI, and dementia. These different categories should be better-considered part of a continuum and not as separate and independent entities. Importantly, some cognitively unimpaired individuals may report subjective cognitive decline and even demonstrate a very subtle decline in serial cognitive testing (Jack et al., 2018).

1.1.1. Subjective cognitive complaints and Subjective Cognitive Decline (SCD)

The SCD category encompasses older adults that complaint and show some concern about their cognitive performance, even though they do not seem to have a significant objective impairment (Mitchell et al., 2014). Extensive community-based studies have pointed to a prevalence of cognitive complaints in older adults of 50% (Singh-Manoux et al., 2014) to 60% (Holmen et al., 2013), and it increases with age (Mitchell, 2008).

Subjective cognitive complaints have been studied for their potential value in predicting the development of clinically relevant conditions (Burmester et al., 2016). A recent meta-analysis found small but significant associations between subjective cognitive complaints and objective cognitive function, although there was limited substantial heterogeneity between studies and evidence of potential publication bias (Burmester et al., 2016).

Participants with subjective cognitive complaints showed an increased risk of non-normative cognitive decline and eventual progression to MCI (Masters, et 2015a) and dementia, especially AD (Gifford et al., 2014; Jessen et al., 2011; Mitchell et al., 2014; Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Therefore, subjective cognitive complaints seem to be associated

to AD and other non-AD dementias (Jessen et al., 2011; Reisberg, Shulman, Torossian, Leng & Zhu, 2010), and could be an earlier marker of the disease, between full compensation and very first decline (Jessen et al., 2014). However, the results of current studies are highly heterogeneous with regard to the rate of decline and risk of conversion to dementia (Burmester et al., 2016; Mitchell et al., 2014). This could be partly due to a dearth of common terminology, different questionnaires used to assess subjective cognitive complaints, and different research environments (Burmester et al., 2016; Molinuevo et al., 2017; Rabin et al., 2015). Jessen et al. (2014) have suggested to encode relevant characteristics in order to improve the predictive validity of the SCD : age of onset of SCD, onset of SCD (number of years), feeling of worse performance than others, memory complaints, concerns associated with SCD, presence of the APOE ε4 genotype, biomarker evidence for neurodegeneration, as well as the confirmation of cognitive decline by others. It should be noted, however, that other personal and health characteristics may also lead to these subjective complaints (e.g. symptoms of depression and anxiety or personality traits such as neuroticism and anxiety) (Jessen et al., 2014).

Subjective Cognitive Decline (SCD) is a new diagnostic entity that characterizes individuals with recent and significant subjective cognitive complaints and free of objective cognitive impairment (Jessen et al., 2014, 2020; Molinuevo et al., 2017). The National Institute on Aging and Alzheimer's Association (NIA-AA) preclinical working group has included SCD as a feature (Sperling et al., 2011), highlighting its importance in disease detection and prevention of MCI and dementia.

The Subjective Cognitive Decline Initiative (SCD-I) published research criteria for SCD in the context of preclinical AD (Jessen et al., 2014, 2020) (Table 1).

Table 1
Criteria for SCD

A) Inclusion criteria (both should be present):
1. Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.
2. Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI or prodromal AD.
B) Exclusion criteria (both should be present):
1. MCI, prodromal AD, or dementia.
2. Can be explained by a psychiatric or neurologic disease (apart from AD), medical disorder, medication, or substance use.

1.1.2. Mild Cognitive Impairment (MCI)

MCI has been considered a transactional or intermediate state between healthy aging and dementia (Petersen, 2004). MCI is a complex concept, and its limits and definition have been revised several times (Ganguli, 2014; Petersen et al., 2018). The American Academy of Neurology (ANN) guideline remarks that an appropriate MCI diagnosis is critical because MCI becomes increasingly common as individuals age and is associated with an increased risk of dementia. In a recent study MCI participants had a ten-fold higher risk of conversion to dementia than the general population, suggesting that many are actually in a pre-dementia phase of the

illness (Gauthier et al., 2011). Therefore, it is possible that this condition implies a pathological disease rather than normative cognitive aging (Petersen et al., 2018).

Reisberg et al. introduced the term MCI in 1988 to describe individuals scoring three in the Global Deterioration Scale (GDS) (Reisberg, 1988). In 1999, Petersen and his colleagues from the Mayo Clinic established MCI clinical criteria. The conceptualization enabled the differentiation of MCI from other diagnostic categories, such as preclinical dementia (Petersen et al., 1999). Importantly, in 2004 (Winblad et al., 2004), the MCI criteria established differences between MCI subtypes, depending on the number and type of the cognitive domains affected: Single domain amnestic MCI (only memory); multidomain amnestic MCI (memory and other domains); single domain non-amnestic MCI (only one domain, different from memory); and multidomain non-amnestic (two or more cognitive domains, different form memory).

Previous studies have reported that amnestic MCI usually evolves to AD (Clark et al., 2013; Petersen et al., 2001; Vos et al., 2013). Consequently, Dubois & Albert (2004) developed clinical criteria for MCI of Alzheimer-type or prodromal AD, including neuroimage and biomarkers, to establish the diagnosis.

After several controversies, the NIA-AA working groups for the diagnosis of MCI proposed consensus criteria (Albert et al., 2011) (Table 2). They referred to this state as "MCI due to AD" and included a more consistent use of biological tests to support and maximize the diagnosis.

Table 2
MCI to AD diagnostic criteria established by the NIA-AA

A) Establish clinical and cognitive criteria.
   1. Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time).
   2. Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains). Scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data (i.e., for the impaired domain(s), when available). It is emphasized that these ranges are guidelines and not cut-off scores.
   3. Preservation of independence in functional abilities.
   4. Not demented

B) Examine etiology of MCI consistent with AD pathophysiological process.
   1. Rule out vascular, traumatic, medical causes of cognitive decline, where possible.
   2. Provide evidence of longitudinal decline in cognition, when feasible.
   3. Report history consistent with AD genetic factors, where relevant.

The *Diagnostic and Statistical Manual of Mental Disorders - fifth edition* (DSM-5) (APA, 2013) includes a characterization of "Mild Neurocognitive Disorder" that corresponds to the MCI concept (Table 3).

Table 3
DSM-5 diagnostic criteria for Mild Neurocognitive Disorder

A) Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on:
1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and,
2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. Performance typically lies in the 1-2 standard deviation range (between the 3rd and 16th percentiles).
B) The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
C) The cognitive deficits do not occur exclusively in the context of a delirium.
D) The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Over the past decades, higher estimates of prevalence have been reported due to the expansion of MCI's definition (Hu et al., 2017). Nevertheless, there are some discrepancies between authors (Canevelli et al., 2016; Luck, Luppa, Briel, & Riedel-Heller, 2010; Mitchell & Shiri-Feshki, 2009; Nie et al., 2011). Recent meta-analyses have been published to overcome this limitation. A meta-analysis of studies published between 1999 and 2016 (Hu et al., 2017) estimated an MCI prevalence of 16% in clinical populations and of 14% in population-based settings. However, it is essential to note that significant heterogeneity was observed, indicating substantial inconsistency among different publications. Similarly, in another meta-analysis, Petersen et al. (2018) estimated and MCI prevalence of 6.7% for ages 60–64, 8.4% for 65–69, 10.1% for 70–74, 14.8% for 75–79, and 25.2% for 80–84.

In Spain, some differences in prevalence estimation between studies were also observed. In a population-based study of older adults, the overall prevalence of MCI was 9.6% (Lara et al., 2016). However, Gavrila et al. (2009) estimated a prevalence of 14.5%, including both community dwellers and institutionalized elders from rural and urban areas. The findings of Lopez-Anton (2015) were even lower, with a prevalence of 7.93% of MCI using Petersen's criteria (Petersen et al., 1999) and of 3.72% using the DSM-5 (APA, 2013). Lopez-Anton et al. (2015) argued that the operational criteria of MCI used in their report were not harmonized for comparative studies and that sampling differences increase the heterogeneity between research studies. In Galicia, Juncos-Rabadán et al. (2014) estimated an MCI prevalence of 31.4% in patients aged 50 years and older from primary care health centers with subjective cognitive complaints. This percentage is higher than the reported in previous studies in our country (Gavrila et al., 2009; Lara et al., 2016; Lopez-Anton et al., 2015), probably because the study was performed with a clinical sample.

1.1.3. Dementia due to Alzheimer's Disease (AD)

AD is the most common type of dementia and, like other neurodegenerative dementias, can be considered the end of a continuum that begins with cognitive decline that usually progresses slowly over time, and lasting several years or decades (Jack et al., 2013; Vellas et al., 2011). Its estimated prevalence is 10-30% among individuals aged 65 and older, with an incidence of 1-3% (Masters et al., 2015b). Long preclinical and prodromal phases characterize AD. Findings from studies on patients suffering from the autosomal dominant version of AD and population studies that have followed participants or analyzed their performance retrospectively have suggested that the disease probably starts at least 10–15 years earlier than when patients typically receive their diagnosis (Bateman et al., 2012). This late diagnosis implies impediments to research, limiting the ability to identify the early mechanisms that trigger the disease and contribute to the conversion.

The DSM-5 (APA, 2013) has redefined the cognitive disorders associated with aging. In this new version, the term "Major Neurocognitive Disorder" equates to dementia. Criteria for Mayor Neurocognitive Disorder are detailed in Table 4. Importantly, dementia type should be specified afterward, being each subtype established according to the underlying etiology, including AD. The DSM-5 (APA, 2013) also includes criteria for Major Neurocognitive Disorder due to AD.

Table 4
DSM-5 criteria for Mayor Neurocognitive Disorder

A) Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. Performance is typically 2 or more standard deviations below appropriate norms (3rd percentile or below).
B) The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
C) The cognitive deficits do not occur exclusively in the context of a delirium.
D) The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

AD diagnostic criteria were initially defined by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup as a clinical-pathological entity, that was diagnosed definitely at autopsy and in life as possible or probable (McKhann, Drachman, Folstein, & Katzman, 1984). In 2011, new diagnostic criteria were published, integrating biomarkers evidence (McKhann et al., 2011).

The NIA-AA published dementia criteria according to the syndromal staging of the cognitive continuum were designed for observational and intervention research (Jack et al., 2018), not for

routine clinical care, in contrast with those of the DSM-5 manual (APA, 2013). The biological definition of AD has been considered key for understanding the underlying mechanisms of this type of dementia during the last years. Thereby, in 2018, the NI-AA (Jack et al., 2018) established that AD refers to Aβ plaques and pathologic tau deposits, defined in vivo by abnormal biomarkers of Aβ and pathologic tau, being both biomarkers required. Importantly, AD diagnosis is only made with certainty after the post-mortem neuropathological examination reveals the presence of amyloid plaques and neurofibrillary tangles in the brain of the patient that has suffered the clinical symptoms before death (Bateman et al., 2012). Thus, the antemortem diagnosis relies on a set of clinical inclusion and exclusion criteria (such as APA, 2013; McKhann et al., 2011).

However, the use of biomarkers has been discussed by researches, and they have not reached the appropriate cost-benefit level in the accurate diagnosis of AD. Post-mortem brain tissues (Price et al., 2009) and clinical imaging studies (Aizenstein et al., 2008) reveal that some controls have a degree of amyloid deposition similar to that in patients with MCI. Further, Gomar et al. (2011), suggested that using all available data to make an accurate prediction would appear optimal in clinical practice or to enrich samples in a clinical trial. Moreover, in a big sample, cognitive markers were consistently more powerful predictors of MCI evolution than brain volumetric and cerebrospinal fluid (CSF) biomarkers (Gomar et al., 2011). Similarly, Palmqvist et al. (2012) concluded that, although screening for biological and cognitive markers slightly improve sensitivity and specificity values, the cognitive markers, obtained through simple screening instruments, are as accurate as the CSF biomarkers.

1.1.4. Risk factors and predictors of progression to AD

Both, SCD and MCI can also lead to other disease processes different from dementia, for example, other neurologic, neurodegenerative (including other types of dementia), systemic, or psychiatric disorders (Jessen et al., 2011; Petersen et al., 2018; Reisberg et al., 2010). Likewise, some MCI and specially SCD participants do not even show progress in cognitive decline and, conversely, may remain stable or revert to cognitively unimpaired (Ávila-Villanueva, Maestú, & Fernández-Blázquez, 2018; Facal et al., 2015, 2019; Petersen et al., 2018).

A recent clinical study (Bessi et al., 2018) estimated that, at a seven-year follow-up, 26 out of 109 SCD subjects (24%) had converted to MCI and 15 (14%) had converted to AD. Since SCD is a new diagnostic entity, more studies are necessary to establish the conversion rate.

Regarding MCI, in Hu et al. (2017) meta-analysis, the estimated progression rates were 45% stable MCI, 15% reversion to cognitively unimpaired, 34% progression to dementia, and 28% progression to AD. There was an increase in the stable and reversion rates in community-based populations compared with the clinic-based, while dementia and AD rates exhibited a decrease.

Similarly, Petersen et al. meta-analysis (2018) estimated a cumulative dementia incidence of 14.9% in MCI participants who were older than 65 years and were followed for two years. At 2-5 years after, the relative risk of all types of dementia was 3.3, and the relative risk of AD 3.0. Importantly, MCI individuals who revert were at higher risk of progression back to MCI or dementia than individuals who have never received an MCI diagnosis.

In our context, Marcos et al. (2016), in a Spanish population-based study of 4.5 years of follow-up, estimated that approximately 15% of the participants with a diagnosis of MCI based

on DSM-5 criteria (APA, 2013) and approximately 10% of the participants with a diagnosis of MCI based on Petersen's criteria (Petersen et al., 1999) developed dementia.

Besides, studies from different countries (Brodaty et al., 2013; Nordlund et al., 2010) have concluded that in the multi-domain amnestic MCI group, the rate of transition to normal functioning is lowest, and the conversion to dementia the highest of all MCI groups.

One major challenge is to identify which are the early markers for AD dementia in SCD and MCI participants, to differentially predict those individuals who will progress from those who will remain stable. Several reviews and meta-analysis have addressed this issued (Baumgart et al., 2015; Belleville et al., 2017; Cooper, Sommerland, Lyketsos & Livingstone, 2015; Li et al., 2016) and diverse risk factors have been identified. Some demographic characteristics (i.e. older age, female) and biological conditions (genetics, structural and functional neurological abnormalities, and cytotoxicity proteins) have been associated with a higher risk of progression (Li et al., 2015). Results have suggested that APOEε4 increases the risk of AD dementia. Furthermore, findings indicated that abnormal concentration of defective Tau and amyloid-β in CSF have been associated with a high risk of conversion from MCI to AD. Concerning MRI, results suggested that MCI patients with hippocampal atrophy, medial temporal lobe atrophy, entorhinal atrophy, and white matter hyperintensities volume had a significantly higher incidence of AD than those without.

Lifestyle factors have also been identified as risk factors of dementia. Regarding to the smoking habit, inconsistent results have been found. A meta-analysis of prospective cohort studies (Zhong, Wang, Zang, Guo & Zhao 2015) found a significantly increased risk, whereas another meta-analysis (Cooper et al., 2015; Li et al., 2016) did not find this relationship significant, especially after controlling for age, suggesting that this effect was probably due to the competing risk of mortality. Another essential lifestyle factor is alcohol consumption. A recent meta-analysis (Cooper et al., 2015) concluded that massive alcohol abuse predicts conversion from any MCI to dementia. However, the authors concluded that there were inconsistences about whether moderate alcohol consumption could predict dementia.

Cardiovascular risk factors have been examined in different studies of dementia progression (Baumgart et al., 2015; Cooper et al., 2015; De Felice & Ferreira, 2014; Li et al., 2016; Power et al., 2011; Yang & Song, 2013). Studies have concluded that diabetes increases the risk of AD and dementia in participants with MCI (Baumgart et al., 2015; Cooper et al., 2015; Li et al., 2016). Importantly, evidence across epidemiological and clinical studies appeared consistent (Cooper et al., 2015). Some findings suggest that diabetes increases dementia risk not only through vascular pathways but also through interactions with other biological mechanisms related to diabetes itself (De Felice & Ferreira, 2014; Yang & Song, 2013). The evidence regarding hypertension is inconsistent (Cooper et al., 2015; Li et al., 2016). Some findings indicate that high blood pressure does not predict progression from any-type MCI to all-cause dementia, but evidence regarding MCI to AD is inconsistent (Cooper et al., 2015). Systematic reviews and meta-analyses of hypercholesterol, also called hyperlipidemia, have concluded that there is mixed evidence for the relationship between high cholesterol levels and dementia (Baumgart et al., 2015).

Moreover, moderate and severe traumatic brain injury should also be mentioned as a risk factor of dementia (Bergamo, 2014; Gardner & Yaffe, 2014). Thus, those who experience repeated head injuries (such as combat veterans, football players, and boxers) at a higher risk of dementia (Lehman, Hein, Baron & Gersic, 2013; Smith et al., 2013).

Besides, it is vital to highlight the role of years of formal education (Baumgart et al., 2015). Although a meta-analysis concluded that the amount of education does not reduce the risk of progression from any MCI to all-cause dementia (Cooper et al., 2015), further evidence has identified that years of schooling delays the manifestation of dementia symptoms (Beydoun et al., 2014; Meng & D'Arcy, 2012). Therefore, illiterate participants or people with a low level of education would present a higher risk of manifesting dementia symptoms than those with greater literacy.

Neuropsychological measures have been studied as early markers of AD dementia. A recent meta-analysis (Belleville et al., 2017) concluded that verbal memory measures and many language tests (naming and semantic fluency) yielded a very high predictive accuracy. Moreover, most measures of verbal memory were barely influenced by the testing conditions. Other domains, such as executive functions and visual memory, showed better specificity than sensitivity. Predictive accuracy was highest when combining memory measures with a small set of other domains, especially executive function and language, or when relying on broad cognitive batteries.

Lastly, ABS have also been mentioned in different studies as a risk factor for all-type dementia and AD, in SCD and MCI participants, both in clinical and community settings (Banks et al., 2014; Connors et al., 2017; David et al., 2016; Donovan et al., 2014; Geda et al., 2014; Masters et al., 2015a; Mortby & Anstey, 2015; Pink et al., 2015; Pocnet et al., 2015). Depression is one of the most frequent ABS and has been the most studied symptom in recent years (Ismail et al., 2017b). Findings have suggested a significant link between subjective cognitive complaints and depression (Burmester et al., 2016) whereas in MCI, depression has been associated with an increased risk of dementia (Gonzales et al., 2017; Singh-Manoux et al., 2017), and AD (Gonzales et al., 2017).

1.2. AFFECTIVE AND BEHAVIORAL SYMPTOMS (ABS)

ABS are non-cognitive, psychological symptoms that include disturbances of mood, perception, and behavior related to a neurocognitive disorder (Lyketsos et al., 2011). The NIA-AA research framework (Jack et al., 2018) has defined ABS as symptoms attributable to mood or psychological disorders, such as anxiety, depression, or apathy.

ABS were associated with significant functional impairment (Apostolova et al., 2014; Fischer, Ismail, Schweizer, 2012), higher burden (Ng et al., 2017) and significant caregiver stress (Fischer et al., 2012), reduced quality of life (Karttunen et al., 2011), and worse clinical course (Wergeland, Selbæk, Bergh, Soederhamn, & Kirkevold, 2015). Moreover, the presence of ABS were linked to more rapid cognitive decline, earlier institutionalization, and higher mortality rates (Cieslak, Smith, Lysack, & Ismail, 2018; Lanctôt et al., 2017).

ABS are highly prevalent in dementia (Selbæk, Engedal & Bergh, 2013) and AD (Zhao et al., 2016). Thus, meta-analytical evidence (Selbæk et al., 2013) showed that the weighted mean prevalence of having at least one ABS in dementia, throughout the course of the disease, was 82%. However, the frequency reports vary considerably between studies probably due to large differences in methodology, case selection, and assessment procedures (Selbæk et al., 2013; Van der Linde et al., 2016). Studies have concluded that the most common ABS in AD is apathy (Aalten et al., 2007; Fernández-Martínez et al., 2008; Zhao et al., 2016), with an estimated prevalence of 49% in a recent meta-analysis (Zhao et al., 2016).

For the first time in 2018, the NIA-AA dementia criteria (Jack et al., 2018) call attention to ABS, stating that although cognitive impairment is the core clinical criteria, neurobehavioral disturbances may be a prominent characteristic of the clinical presentation

Recently, a professional interest area (PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART) have identified the later-life onset of sustained ABS as an increased risk of cognitive decline and dementia (Ismail et al., 2016; Ismail et al., 2017a).

1.2.1. Mild Behavioral Impairment (MBI) criteria

In 2016, it was published diagnosis criteria for Mild Behavioral Impairment (MBI) (see Table 5) that operationalized the identification and assessment of later life emergent, sustained, and, frequently, subtle ABS in pre-dementia states (Ismail et al., 2016). With these criteria, researchers intended to standardize research into early non-cognitive markers of dementia. Thus, MBI is considered an at-risk state for incident cognitive decline and dementia and could be the index manifestation of neurodegeneration observed in advance of cognitive impairment (Taragano et al., 2018).

Importantly, the criteria specified later life emergence of symptoms with minimum six months duration, increasing signal detection, and minimizing false positives from the inclusion of transient and reactive states and formal psychiatric illnesses such as adjustment disorder.

MBI criteria also specify at least minimal impairments in interpersonal relationships, other aspects of social functioning, or ability to perform at the workplace as a result of the ABS as opposed to cognitive symptoms.

Table 5
ISTAART research diagnostic criteria for MBI

A) Changes in behavior or personality observed by patient, informant, or clinician, starting later in life (age +50 years) and persisting at least intermittently for more than six months. These represent clear change from the person's usual behavior or personality as evidenced by at least one of the following:

1. Decreased motivation (e.g., apathy, aspontaneity, indifference).
2. Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability).
3. Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind).
4. Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits).
5. Abnormal perception or thought content (e.g., delusions, hallucinations)

B) Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:

1. Interpersonal relationships.
2. Other aspects of social functioning.
3. Ability to perform in the workplace.

The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.

C) Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.

D) The patient does not meet criteria for a dementia syndrome (e.g., AD, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

Importantly, MBI distinguishes between formal psychiatric illness or chronic psychiatric symptomatology. These new-onset psychiatric symptoms are the core of the MBI construct. Historically elderly participants with later onset ABS, who did not show obvious cognitive impairment would receive a psychiatric diagnosis, being the possibility of the neurodegenerative disease often overlooked (Cieslak et al., 2018; Wooley et al., 2011). This population has been traditionally excluded from observational cohorts and disease-modifying dementia clinical trials (Mortby et al., 2018a).

Five domains were proposed for the MBI assessment: decreased motivation (Sherman, Liu, Herrmann & Lanctôt, 2018); affective dysregulation (Ismail et al., 2018); impulse dyscontrol; social inappropriateness (Desmarais, Lanctôt, Masellis, Black, & Herrmann, 2018); and abnormal perception or thought content (Fischer & Agüera-Ortiz, 2018).

1.2.1. Apathy

Apathy has been defined primarily by a marked loss of motivation and drive, that is not attributable to emotional distress, intellectual impairment, or diminished level of

conscientiousness (Marin, 1990, 1991). The International Apathy Workgroup Consensus Diagnostic Criteria has established three separate dimensions of apathy symptomatology: cognitive, affective, and behavioral (Robert et al., 2009).

Apathy is a common symptom in pre-dementia states (Sherman et al., 2018), with a prevalence in cognitively unimpaired participants ranging from 1.4 to 7.6% (Chan et al., 2010; Fernandez-Martinez et al., 2010; Geda et al., 2008; Onyike et al., 2007) and is a behavioral trait commonly observed in older adults (Ishii, Weintraub & Mervis, 2009).

Apathy may be easily confounded with depression. It is important to note that although both symptoms share diminished interest, psychomotor retardation, fatigue/hypersomnia and lack of insight, symptoms of dysphoria, self-criticism, suicidal ideation, pessimism, feeling guilty and hopelessness are unique to depression (Ishii et al., 2009). Importantly, the overlap between apathy and depression is an area of controversy. Patients with apathy may be wrongly diagnosed with depression, leading to further confusion around the phenomenology (Newson et al., 2010). Because of that, Apathy in MCI can be particularly tricky to identify and diagnose, with prevalence rates from 3.1 from 50.5% depending also on the chosen population and instrument (Fernandez-Martinez, Molano, Castro & Zarranz, 2010; Geda et al., 2008; Onyike et al., 2007; Sherman et al., 2018)..

Apathy is associated with the reduced daytime activity (Kuhlmei, Walther, Becker, Müller, & Nikolaus, 2013), weight loss (Volicer, Frijters, & Van der Steen, 2013), caregiver burden (George, Withfield, & Walker, 2013) and cognitive decline (Zahodne & Tremont, 2013). Besides, apathy is an independent risk factor for the progression from MCI to AD (Richard et al., 2012; Somme, Fernández-Martínez, Molano, & Zarranz, 2013).

1.2.2. Affective and emotional dysregulation

Affective and emotional symptoms include anxiety, worry, depression, dysphoria, changeability, euphoria, and elation (Ismail et al., 2016). They are common symptoms in normal aging, preclinical and prodromal dementia (Fiske, Wetherell & Gatz, 2009; Peters et al., 2012), and are associated with poorer outcomes overall (Cerejeira, Lagarto, & Mukaetova-Ladinska, 2012), functional impairment, and decreased cognitive and psychosocial function (Karttunen et al., 2011). Several studies (Creese et al., 2019b; Sheikh et al. 2018) reported that impairments in the affective and emotional regulation domain were the most common in MBI.

Among the ABS, depression has been the most studied (Ismail et al., 2017b). It has been associated with apathy (Ruthirakuhan, Herrmann, Vieira, Gallagher, & Lanctôt , 2019), sleep disorders (Xian et al., 2015), anxiety (Burke, Cadet, Alcide, O'Driscoll, & Maramaldi , 2018) and appears to be related to neurodegenerative processes in older adults (Lauriola et al., 2018; Ruthirakuhan et al., 2019). A systematic review and meta-analysis of studies of depression in latest life (75 and older) (Luppa et al., 2012) found that the prevalence of major depression ranged from 4.6 to 9.3% and of depressive disorders from 4.5 to 37.4%. A longitudinal study in patients older than 60 years found that depression ranged to 1.1 to 34.4% (Burns et al., 2012).

Affective and emotional symptoms showed prognostic utility in cognitively unimpaired individuals and MCI for several dementia subtypes (Barnes et al., 2012; Geda et al., 2014; Steenland et al., 2012). ABS symptoms in this domain are often precursors of progressive cognitive decline (Almeida, Hankey, Yeap, Golledge, & Flicker, 2017; Donovan et al., 2014;

Geda et al., 2014; Gonzales et al., 2017; Singh-Manoux et al., 2014; Tapiainen, Hartikainen, Taipale, Tiihonen, & Tolppanen, 2017).

1.2.3. Impulse dyscontrol

This domain contains symptoms as agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, and stimulus bind. However, little data is addressing these ABS in pre-dementia states (Ismail et al., 2018). Importantly, irritability can be regarded as a mood disturbance or a behavioral dysregulation/impulsiveness, since there is support for both possibilities from cluster analyses (Leoutsakos, Forrester, Lyketsos, & Smith, 2015). Among neurobehavioral disease, irritability is a common symptom (Peters et al., 2013) that is associated with a burden on patients, caregivers, and the community alike (Sousa et al., 2016). Irritability was pointed out as one of the ABS that portends the most rapid decline in several datasets (Forrester et al., 2016; Geda et al., 2014; Leoutsakos et al., 2015).

1.2.4. Social inappropriateness

Social inappropriateness includes symptoms as lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits, or inappropriate affect (Desmarais et al., 2018; Ismail et al., 2016). These symptoms are related to social cognition, the ability to process social information coming from others, such as emotions, making inferences about what others may think, and respond appropriately to them (Henry, Von Hippel, Molenberghs, Lee, & Sachdev , 2016). Through different manifestations, social inappropriateness was suggested as one of the first signs of an unrecognized neurocognitive process of decline, even before noticeable impairment on the classical neuropsychological test and brain atrophy (Desmarais et al., 2018). MBI participants with social inappropriateness symptoms can sometimes come to clinical attention after having problems with the law, such as shoplifting or performing unsolicited touching (Liljegren et al., 2015).

1.2.5. Abnormal perception or thought content

This domain includes hallucinations and delusions (Ismail et al., 2016). Psychotic symptomatology is more common in pre-dementia stages than previously understood (Fischer & Agüera-Ortiz, 2018; Köhler et al., 2013; Ribe et al., 2015). In the MBI-C, the abnormal perception or thought content was the least common domain, with a frequency of 3% in the self-reported and of 6% in the informant-reported versions of the instrument (Creese et al., 2019b). The least common symptoms were those related to hallucinations present in 1% of the non-dementia non-MCI participants. However, it must be considered that patients and caregivers may be reluctant to divulge information about psychotic symptoms due to stigmatization and clinical trials commonly exclude patients with psychosis (Ropacki & Jeste, 2005).

Recent research suggests that there is a higher risk of dementia in participants with pre-existing severe mental disorders with psychotic symptoms (Ribe et al., 2015). Furthermore, these patients may be more likely to present to memory clinics due to paranoia and suspiciousness (Fischer & Agüera-Ortiz, 2018).

In dementia, psychosis is associated with mortality, progression to dementia, and cognitive decline (Fischer & Sweet, 2016). Hence, patients with a primary psychiatric disorder appear to be at increased risk of neurocognitive disease (Zilkens, Bruce, Duke, Spilsbury, & Semmens, 2014).

1.2.2. Assessment of Affective and Behavioral Symptoms (ABS)

There are a wide variety of instruments to assess ABS in dementia patients considering a diverse and heterogeneous set of behavioral disorders. ABS instruments not only differ in what is assessed (for example, a symptom of a particular ABS domain or symptom domains), but also in some characteristics such as the targeted informant (patient, clinician or caregiver, for example) and the rating approach used (i.e., severity, frequency or other) (de Medeiros et al., 2010). Gitlin, Marx, Stanley, Hansen, & Van Haitsma (2014) have suggested that this may reflect a lack of consensus on what constitutes ABS and how behaviors should be identified, characterized, classified, and assessed. Differences in the sensitivity and specificity of the scales to detect changes after intervention recommend selecting scales based on their anticipated effect size to treatment (Ismail et al., 2013).

Considering the systematic review carried-out by Gitlin et al. (2014), including 16 global and 29 specific scales to measure ABS, it is not possible to determine if one instrument is superior to another. The authors recommend that the selection of an ABS measure should be context-specific and dependent on several key factors that determine the purpose of measurement: if there is a need for a general screen or a more targeted behavioral assessment, the type of setting, who will perform the assessment (patient, informant, clinician), how the assessment will be conducted (for example observation or interview) and the amount of time and resources that are available (Gitlin et al., 2014). It has also been suggested (Gitlin, Kales, & Lyketsos, 2012) to start with general ABS measures, which serve as an all-purpose screen, for a wide range of symptoms. Based on the findings, specific behavioral-targeted scales can be used in follow-up evaluations to provide higher specificity to the types of behaviors manifested, thus obtaining a more nuanced understanding (Gitlin et al., 2012, 2014).

The following section describes the most commonly used instruments to measure ABS, namely, Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI), and Mild Behavioral Impairment Checklist (MBI-C). Although its detailed description exceeds the limits of this work, it should be noted that there are other instruments available to provide global (e.g. Behavioral Pathology in Alzheimer's Disease -Behave-AD- (Reisberg, Auer, & Monteiro, 1996)) and specific (Apathy Inventory –AI- (Robert et al., 2002) Cohen-Mansfield Agitation Index –CMAI- (Cohen-Mansfield, Marx, & Rosenthal 1989)) measures of the ABS.

Some instruments assess global measures of ABS, such as the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), and the Mild Behavioral Impairment Checklist (MBI-C) (Ismail et al., 2017a), while others are focused on specific measures, such as the Geriatric Depression Scale (GDS) (Sheikh & Yesavage, 1986; Yesavage et al., 1982). Importantly, the GDS, despite being a specific measure, is commonly used in research studies given the high prevalence of depressive symptomatology in older adults (Ismail et al., 2018; Ismail et al., 2017b). On the other hand, the NPI (Cummings et al., 1994) is the most widely used ABS global measure in clinical and research settings (Ismail & Mortby, 2017). Finally, the MBI-C (Ismail et al., 2016) is a new instrument specially designed to assess ABS in pre-dementia states.

1.2.2.1. Geriatric Depression Scale (GDS)

The GDS, in its original form of 30 item (GDS-30) and in its shorter version of 15 items (GDS-15), is the most popular scale for screening late-life depression (Mitchell, Bird, Rizzo, & Meader, 2010).

The GDS-30 (Yesavage et al., 1982) is a valid and reliable self-reported depression scale for elderly people. It uses a simple yes/no format and comprises 30 questions, 20 indicating the depression when they are answered positively and ten when they are answered negatively. The scale is simple to administer, not requiring the time or skills of a trainer interviewer. Hence, the scale was designed for healthy and unhealthy participants, including people with cognitive impairment and dementia.

The GDS-30 has demonstrated to be a valid and reliable instrument. The median correlation between the items of the GDS-30 and the corrected-items total score was 0.56, with a range of 0.32-0.83, suggesting all the items measure a common latent variable. The inter-item correlation among the items was 0.36, indicating high internal consistency. Besides, the Cronbach's alpha coefficient was high, 0.94. The split half-reliability coefficient was 0.94 and the test-retest reliability 0.85 ($p < 0.001$). The convergent validity of the GDS with the Self-Rating Depression Scale (SDS) (Zung, 1965) was 0.84 and 0.83 with the Hamilton Rating Scale for Depression (HRS-D) (Hamilton, 1967).

To reduce fatigue and avoid concentration problems in the elderly, a shorter version of the GDS comprising 15 items was developed (Sheikh & Yesavage, 1986). The GDS-15 included the items that had the highest correlation with depressive symptoms. The scale maintained the yes/no format and included ten items that indicated depression when answered positively, while the rest indicated depression when answered negatively.

The GDS-15 has been adapted and validated into Spanish (Martínez et al., 2002), showing good intra-rater ($r= 0.95$; $p <0.001$) and internal consistency (Cronbach's α: 0.99; $p <0.001$), and acceptable between-rater reliability ($r= 0.65$; $p <0.001$). The area under the curve in distinguishing depression patients was 0.83 (sensibility: 81.1%; specificity: 76.7%), with a cut-off of five or more points. The convergent validity reached a coefficient of 0.62 ($p <0.001$) when the GDS-15 and the Montgomery-Asberg score were correlated (Montgomery & Asberg, 1979). The divergent validity, which was obtained by correlating the score on the GDS-15 with the Spanish version of the Short Portable Mental Status Questionnaire (SPMSQ) (Martínez et al., 2001), was below the .30 threshold ($r= 0.23$ p <0.001). Thus, the reliability and validity levels were good and similar to the original instrument.

1.2.2.2. Neuropsychiatric Inventory (NPI)

The NPI (Cummings et al., 1994) is a structured informant interview which provide a subjective assessment about the presence, frequency and severity of ten ABS (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, and aberrant motor behavior) and two neurovegetative domains (sleep and nightmare behavior change and appetite/eating change). The caregiver also informs about the level of distress that him/herself is suffering concerning that specific symptom domain.

Different relevant methodological approaches to ABS are addressed by this instrument (de Medeiros et al., 2010):

1. Items are behavior-based and observable, facilitating informant reports.
2. The items are grouped into domains under screening questions to enable quick completion and interpretation of results.
3. Items are specific to dementia populations.
4. Standardized rating of domain frequency, severity, and caregiver distress.

The validation analyses (Cummings et al., 1994) of the NPI have demonstrated that the instrument has good psychometric properties. Results from the Delphi panel showed that each group of questions, except form those assessing aberrant motor behavior, received scores of less than two, indicating high content validity. Besides, the NPI was compared with the appropriate scales of the Behave-AD (Reisberg et al., 1996) and the total score of the HRS-D (Hamilton, 1967). All the correlations were moderately high and reached the significance level, indicating excellent concurrent validity. The internal consistency (Cronbach's α: .88) and between-rater agreement (Frequency: r= 0.93-1.0; Severity: r= 0.89-1.0) were high. Finally, the test-retest reliabilities of all scored measures were significantly correlated (Frequency: r= 0.79; Severity: r= 0.86).

Some psychometric properties of the Spanish version of the NPI have also been examined (Vilalta-Franch et al., 1999). The alpha index indicated good internal consistency (Cronbach's α = 0.85). Regarding the between-rater agreement, the items obtained phi values that varied between 0.85 and 1; and kappa values between 0.91 and 1.

The NPI-Q (Kaufer, Cummings, Smith, MacMillan, & Shelley, 2000) is a self-administered version of the original NPI scale (Cummings et al., 1994). The NPI-Q is one of the most commonly used rating scales for ABS (Ismail, Agüera-Ortiz, et al., 2017). In the NPI-Q, the caregiver follows written instructions for completing the questionnaire (Kaufer et al., 2000). The 12 symptoms domains (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and nightmare behavior change, and appetite/eating change) are assessed by a screening question derived from the NPI that cover core symptoms manifestations. Informants are asked to circle "yes" or "no" in response to each screening question, and to proceed to the following question if the answer was "no." If the answer was "yes," they have to rate severity on a three-point scale (one mild, two moderate, and three severe) and the caregiver stress scale on an anchored scale from zero to five. Informants usually complete the NPI-Q in five minutes or less. Importantly, the NPI-Q covers a retrospective period of four weeks.

The NPI-Q provides a brief and reliable assessment of ABS and associated caregiver stress (Kaufer et al., 2000). The test-retest reliability of the NPI-Q was acceptable (Severity: r = 0.80; Stress: r = 0.94). Convergent validity, measured with an interscale correlation between the NPI total score and NPI-Q total severity, was 0.91, while with caregiver stress was 0.92.

The Spanish version of the NPI-Q (Boada et al., 2002) also has good psychometric properties. Test-retest reliability was high (Severity: r = 0.89; Stress: r = 0.90). Convergent validity between NPI and NPI-Q was also high (Severity: r = 0.88; Stress: r = 0.92).

1.2.2.3. The Mild Behavioral Impairment - Checklist (MBI-C)

The traditional scales, as the NPI, the CMAI or the Behave-AD, were originally developed for dementia patients and clinical settings, and therefore use reference times of two or four weeks, time frame too short for the detection of neurodegenerative prodromal symptoms (Ismail et al., 2017a). Given the transient nature of ABS (Selbæk, Engedal, Benth & Bergh 2014), a more extensive observation will be more appropriate, since it will allow time for reactive states to pass (e.g., arising from adversity, sleep deprivations or medications) (Ismail et al., 2017a). As a result of this need for a measure with a broad scope and sufficient reference time, researchers developed the MBI-C (Ismail et al., 2017a).

The MBI-C represents a potential advancement over the existing scales because the instrument mandates symptoms being late-life in onset and sustained for six months. Hence, the MBI-C was designed for a community-dwelling functionally independent, elderly population, to ensure relevance to prodromal and preclinical populations.

The MBI-C was explicitly designed to operationalized MBI. MBI-C is a case ascertainment tool based on ISTAART-AA criteria (Ismail et al., 2016). The instrument identifies ABS in pre-dementia states, such as SCD and MCI. Therefore, it could be useful to predict conversion to dementia, including AD. The MBI-C provides an inexpensive method for capturing ABS in a higher-risk population for cognitive decline and dementia.

The MBI-C is a brief instrument that can be completed in 8 minutes approximately. The MBI-C includes 34 items distributed in five domains: decreased motivation (six questions, including assessments of cognitive, behavioral, and emotional apathy); 2) affective dysregulation (six items, including low mood, anhedonia, hopelessness, and guilt, and one question each for worry and panic); 3) impulse dyscontrol (12 items describing agitation, aggression, impulsivity, recklessness, and abnormal reward and reinforcement); 4) social inappropriateness (five items assessing sensitivity, empathy, and tact); 5) abnormal thought and perception (five questions assessing suspiciousness, grandiosity, and auditory and visual hallucinations). For each item, a "yes" or "no" question is followed by a severity rating scale of 1- mild, 2-moderate, or 3-severe. Importantly, symptoms should represent a meaningful change from baseline.

The MBI-C is available at www.MBItest.org in different languages, including Spanish (Agüera-Ortiz & López-Álvarez, 2017). However, further studies are still needed to determine the psychometric properties of the instrument (such as reliability, concurrent and predictive validity) in different samples of individuals and cultures.

The MBI may be reported by the clinician, informant or patient (self-reported) that can provide complementary information about ABS (Creese et al., 2019b). In both self-reported and informant-reported version, the most common domains were emotional dysregulation, impulse dyscontrol, decreased interest/motivation, social inappropriateness, and abnormal thoughts and perception (Creese et al., 2019b). Results about MBI-C factor structure are yet inconclusive (Creese et al., 2019b; Cui et al., 2019; Hu, 2019).

A recent validation study in Canada (Hu, 2019) has concluded that the MBI-C has high internal consistency, with a internal consistence above 0.80 for each domain and the total score except for social inappropriateness (Cronbach's α=0.71). Further, the MBI-C and NPI-Q were positively and significantly correlated, indicating convergent validity. In this study with hospital clinic predementia patients, as cognitive disease status worsens, MBI-C scores increased, and MoCA (Nasreddine et al., 2005) decreased (Hu, 2019).

1.2.3. Affective and Behavioral Symptoms in pre-dementia states and its role in progression to dementia

Regarding pre-dementia states, ABS are being increasingly cited as an intrinsic aspect of prodromal dementia and as a marker of impending cognitive decline that precedes the onset of cognitive symptoms, both in MCI and SCD (Mortby & Anstey, 2015). Over the last decade, evidence has suggested that the emergence of ABS in later life increases the risk of cognitive impairment (Banks et al., 2014; Connors et al. 2017; David et al. 2016; Donovan et al., 2014;

Geda et al., 2014; Masters et al., 2015a; Mortby & Anstey, 2015; Pink et al., 2015; Pocnet et al., 2015).

In a self-administrated study of the MBI-C, Creese et al., (2019a) found that MBI diagnosis was associated with a faster decline in attention and working memory. Another study (Gill et al., 2020) reported that ABS measured at baseline and brain morphology measures have prognostic utility for predicting diagnosis in patients with normal cognition or MCI. MBI total score, followed by impulse dyscontrol and affective dysregulation, were the most predictive domains of future diagnosis.

1.2.3.1. Affective and Behavioral Symptoms in SCD

Importantly, in the SCD criteria, it is specified that the symptomatology cannot be explained by a psychiatric or neurological disease (apart from AD), medical disorder, medication, or substance use. In some studies on SCD, participants report subthreshold symptoms of depression and anxiety (Jessen et al., 2014). Nevertheless, they do not necessarily fulfill the criteria for a psychiatric disorder, such as major depression or generalized anxiety, according to DSM-5 (APA, 2013). Hence, among the features suggested by the working group on SCD-I for coding SCD, it is included the assessment of ABS, especially depression and anxiety (Jessen et al., 2014; Molinuevo et al., 2017).

Some literature suggests that SCD may be associated with certain personality traits, especially neuroticism and anxiety (Comijs, Deeg, Dik, Twist, & Jonker, 2002; Dux et al., 2008; Slavin et al., 2010), but until now there is no specific pattern of personality characteristics that at present should be defined as an exclusion criterion (Jessen et al., 2014; Molinuevo et al., 2017).

Some studies have examined ABS in older adults diagnosed as SCD following Jessen et al. (2014) criteria. In a one-year follow-up study (Fernández-Blázquez, Ávila-Villanueva, Maestú, & Medina, 2016), ABS were higher in SCD individuals compared to cognitively unimpaired participants but no differences were found in ABS among converters and non-converters. The authors explain that one possible reason for this unexpected result may be related to the fact that SCD would begin to decline the cognitive status some years before that of psychiatric symptoms. Perrotin et al. (2017) observed a slight but significant increase in depressive symptoms in the SCD-clinic group compared with SCD-community group. This result is in accordance with previous studies that have concluded that increased depressive affect is frequently associated with early cognitive deficits or subsequent dementia (Kaup et al., 2016; Mourao, Mansur, Malloy-Diniz, Castro-Costa, & Diniz, 2016). Hence, the SCD-clinic group showed increases in anxiety and depression compared with controls. Importantly, the co-occurrence of these affective symptoms is not uncommon, especially in elderly individuals (Braam et al., 2014).

The relationship between the presence of subjective complaints and ABS, have been revised in different studies. A meta-analysis (Burmester et al., 2016) showed a significant link between cognitive complaints and depression. Further, ABS's general measures (Donovan et al., 2014; Mewton, Sachdev, Anderson, Sunderland, & Andrews, 2014) and specific measures of anxiety (Balash et al., 2013) are associated with subjective cognitive complaints. Therefore, the early identification of ABS could be an important avenue to explore for early interventions and to prevent cognitive impairment (Mortby et al., 2018a).

1.2.3.2. Affective and Behavioral Symptoms in MCI

First, it is essential to highlight that the ANN guideline on MCI recommends assessing ABS (Petersen et al., 2018). Jack et al. (2018) clinical criteria for MCI established that, thought cognitive performance is the core clinical criteria, ABS may be a prominent feature of the clinical presentation of MCI. A systematic review (Monastero, Mangialasche, Camarda, Ercolani, & Camarda, 2009) and some later studies (Peters et al., 2012; Van Der Mussele et al., 2014) reported that ABS are common in MCI and their prevalence in MCI ranges from 35% to 85% (Apostolova & Cummings, 2008; Monastero et al., 2009).

Besides, Feldman et al. (2004) found that MCI patients with ABS have more significant impairment in global, cognitive, and functional scores than those who have MCI without ABS. ABS in MCI also seems to increase caregiver stress and therefore are more prone to be in clinical care facilities (Ismail, Elbayoumi, et al., 2017).

During the last decade, research studies have suggested that MCI patients with ABS showed a faster progression to dementia (Acosta et al., 2018; Mortby et al., 2017; Peters et al., 2013; Pocnet et al., 2015; Rosenberg et al., 2013) and that ABS are more frequent in participants who develop dementia than in those who do not, both in clinical (Rosenberg et al., 2013) and in population-based settings (Acosta et al., 2018; Mortby et al., 2017).

Longitudinal evidence about the role of ABS in the progression is still scarce. Available evidence pointed-out that MCI participants with any ABS was associated with increased risk of incident dementia, particularly AD (Rosenberg et al., 2013). Another recent population-based study (Acosta et al., 2018) established that the simultaneous presence of two ABS increased to a one-point nine-fold risk of developing dementia, whereas three ABS corresponded to a three-fold. Similarly, Mortby et al. (2017) concluded that ABS symptomatology is related to the three-fold risk of dementia. These results altogether indicate that ABS are essential targets for further research in dementia prevention and prognostication.

Regarding to the most frequently studied ABS, a recent meta-analysis has indicated that depression prevalence observed was 25% and 40%, respectively for MCI community and clinical samples (Ismail et al., 2017b). Both depressive symptomatology and depression diagnosis increase the risk of dementia (Gonzales et al., 2017; Singh-Manoux et al., 2017), especially AD (Gonzales et al., 2017). Researchers have suggested that participants with depressive symptoms may represent a subgroup of MCI that is highly vulnerable to accelerated cognitive decline (Gonzales et al., 2017). Importantly, a recent study concluded that longstanding sustained depression symptomatology did not increase dementia risk, whereas the late onset of depressive symptoms did (Singh-Manoux et al., 2017). These results highlight the importance of an appropriate time window in neurocognitive and psychiatric research (Tapiainen et al., 2017). The relationships between depression and dementia are complex, and while many studies support that depression is a risk factor for dementia, others argue it is a consequence of the disease (Bennett & Thomas, 2014; Byers & Yaffe, 2011). Individuals experiencing the earliest signs of dementia may realize that their function is deteriorating and may have developed depressive symptoms secondary to cognitive decline. The prospect of having an incurable, progressive disease leading to loss of autonomy could understandably lead to depressive symptomatology (Jajodia & Borders, 2011). Importantly, depression and dementia share common etiological factors such as inflammation, vascular changes, and vascular risk factors (Köhler et al., 2010). However, even in research studies which have controlled for shared risk factors, in particular vascular disease,

when evaluating the risk of developing AD in patients with depression (Köhler, van Boxtel, Jolles & Verbey, 2011) it remained as an independent risk factor for this type of dementia.

2. OBJECTIVES AND HYPOTHESIS

The main objectives of the present dissertation were to review and analyze ABS as risk factors for conversion to dementia and to determine the prevalence and some psychometric properties of the MBI-C in a sample of participants in pre-dementia states. The specific objectives were:

1. To review and meta-analyze whether ABS, measured with the NPI/NPI-Q, could predict progression from MCI to dementia in participants diagnosed with MCI at baseline according to diagnostic criteria.
2. To know the prevalence of MBI and some psychometric properties of the phone-administered MBI-C applied to informants and to determine if this instrument is valid to assess ABS in SCD participants.
3. To know the prevalence of MBI and some psychometric properties of the phone-administered MBI-C applied to informants and to determine if this instrument is valid to assess ABS in MCI participants.
4. To determine if NPI-Q scores predict conversion to dementia in MCI participants using a ML approach.

Regarding the first and fourth objective, the formulated hypothesis was:

- ABS symptoms, measured with the NPI or NPI-Q, predict progression from MCI to dementia, although the instrument is not designed for pre-dementia states, which may affect the results.

3. METHODS

My research work consists in four different papers. The first one is a systematic review and meta-analysis focused on whether ABS, measured with the NPI or NPI-Q, could predict progression from MCI to dementia. The second and third studies analyzed some psychometric properties of the MBI-C in two populations of older adults, MCI and SCD. Finally, the last study explores the predictive ability of NPI-Q scores to estimate conversion from MCI to dementia.

3.1. Sample

The samples used in the empirical studies included in this thesis belonged to the first cohort of the Compostela Aging Study (CompAS). This study began in 2008 and finished in 2016. The CompAS was carried out in eight representatives Public Primary Care Health Centers in Galicia, an autonomous region in northwest Spain (total surface area 29 430 km (Valcour, Masaki, Curb & Blanchette, 2000) and population 2 724 500 (Juncos-Rabadán et al., 2012)). Inclusion criteria were:

1. Age 50 years and older
2. Attendance to primary care centers with subjective cognitive complaints spontaneously reported by the patient.

Exclusion criteria were:

1. Prior diagnosis of depression or other psychiatric disturbances following the DSM-5 criteria (APA, 2013).
2. Prior diagnosis of neurological disease, including probable AD or other types of dementia, following the DSM-5 criteria (APA, 2013).
3. Previous brain damage or brain surgery.
4. Undergoing chemotherapy.
5. Prior diagnosis of type II diabetes.
6. Sensory or motor disturbances.
7. Consumption of substances that might affect the normal performance of the tasks.

All patients that fulfilled inclusion and exclusion criteria, and accepted their involvement were included in the study. The study received approval by the Ethics in Clinical Research Committee of the Galician Government. It was carried out following the provisions of the Declaration of Helsinki, as revised in Fortaleza 2013, the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice 1996, and the Rules Governing Medicinal Products in the European Community (Directive 91/507/ EEC). Written informed consent was obtained from all participants before the study, and patient anonymity has been preserved.

Participants were informed at baseline about the longitudinal nature of the study and were contacted for follow-up assessments. They underwent the same extensive cognitive assessment at follow-up and were re-diagnosed by the same research team in three follow-ups (every 18-24 months).

3.2. Instruments

Participants underwent cognitive, affective, and clinical examination conducted respectively by general practitioners, neurologists, and psychogerontologists specialized in cognitive assessment of older adults. Assessment of each participant were completed in a period of three weeks. Diagnoses considered cognitive and clinical variables were reached by consensus at special meetings held by the research team.

A questionnaire on sociodemographic and clinical data was used to obtain information from the patients and/or a family member regarding the following variables: age, years of formal education, marital status, occupation, medical history, reading habits and participation in leisure activities. The Charlson's Comorbidity Index (CCI) (Charlson, Pompei, Ales, & MacKenzei, 1987) was obtained from the medical history to provide information about the health status of the patients. Data on peripheral arterial obstructive disease, diabetes, and hypertension were analyzed separately, taking into account our exclusion criteria.

A short Spanish version of the Questionnaire for Subjective Memory Complaints (QSMC) (Benedet & Seisdedos, 1996) comprising seven items and scored on a Likert scale from 1 to 5 (maximum score 35) was administered to participants and a family member in order to assess the severity of subjective cognitive complaints. The items included were:

1. "Do you forget where you left your things?"
2. "Do you forget the names of people you just met?"
3. "Do you forget the names of close relatives or friends?"
4. "Do you often have a word on the tip of your tongue?"
5. "Are you lost in familiar places where you have been before?";
6. "Are you lost in unfamiliar places where you have been a few times?"
7. "Do you forget things you planned to do?".

The participants' general cognitive functioning was evaluated by the Spanish version (Lobo et al., 1999) of the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), with normal age and education groups. Cognitive impairments were evaluated in several domains (orientation, language, attention, praxis, perception, and executive functioning) by the Spanish version (López-Pousa, 2003; Pereiro et al., 2015) of the Cambridge Cognitive Examination-Revised (CAMCOG-R) (Roth, et al., 1986) and other tests. We assessed:

1. Attention with the Trail Making Test (A) (Reynolds, 2002) and the Attention and Calculation CAMCOG-R subscale.
2. Executive functioning with Trail Making Test (B) (Reynolds, 2002), Phonological verbal fluency (Lezak, 2004) (say in one minute words starting with "p") and the Executive Function CAMCOG-R subscale.
3. Memory with by the Spanish version (Benedet & Alejandre, 1998) of the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan & Thompkins, 1987) (which measures List A Total Recall, and Long-Delay Free Recall) and the Memory CAMCOG-R subscale.
4. Language with the Spanish version of the Boston Naming Test (BNT) (Williams, Mack & Henderson, 1989), semantic verbal fluency (animals) (Lezak, 2004) and the Language CAMCOG-R subscale.

The Lawton and Brody Index was used to evaluate the Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969). This test estimates an individual's performance in certain activities according to self-assessment of information provided by a family member. The

scale indicates the level of dependence according to the amount of help needed. Individuals who did not require any help or assistance in any of the investigated activities obtained the maximum score (eight points) and were considered independent.

ABS were assessed with the Spanish version of the NPI-Q (Boada et al., 2002) and the Spanish version of the GDS-15 (Martínez et al., 2002). We also used the Spanish version of the MBI-C to assess ABS (Agüera-Ortiz & López-Álvarez, 2017). In our region, the population is very dispersed. Therefore, to optimize participant retention, the MBI-C was administered by a phone interview to a relative of the patient.

3.3. Identification of SCD and MCI

SCD was diagnosed following Jessen et al. (2014) criteria and MCI was diagnosed in accordance with Petersen's (Petersen, 2004) criteria, revised by Albert et al. (2011).

The categories of MCI were identified following the criteria proposed by Petersen (2004):

1. Individuals with multiple-domain amnestic MCI (mda-MCI) scored 1.5 SD below age- and education-related norms in the MMSE, and in at least 1.5 SD below age- and education-related norms in two CAMCOG subscales and episodic memory measures (short delay free recall, CVLT).

2. Individuals with single-domain amnestic MCI (sda-MCI), scored 1.5 SD below age- and education-related norms in the MMSE and in episodic memory measures (short delay free recall CVLT).

3. Individuals with multiple-domain non-amnestic MCI (mdna-MCI) scored 1.5 SD below age- and education-related norms in the MMSE, episodic memory preserved but scored 1.5 SD age- and education-related norms in several non-memory CAMCOG-R domains.

4. Individuals with single-domain non-amnestic MCI (sdna-MCI) scored 1.5 SD below age- and education-related norms in the MMSE, with normal memory measures preserved, and scored 1.5 SD below age- and education-related norms in one of the non-memory CAMCOG domains.

3.4. Identification of MBI

Diagnosis of MBI was made via a series of semi-structured interviews and medical records, following all the four ISTAART-AA criteria (Ismail et al., 2016). To determine criterion one, we asked for the presence of symptoms over the last six months in the initial phone interview and then confirmed it using the NPI-Q (administered to an informant on the patient's assessment session). For the NPI-Q, both one month (the proper measure of the instrument) and six-month symptom duration were necessary (as required in the criteria). For criteria two and three, information was obtained from the phone interview. Criterion four was obtained from the final assessment and diagnosis. The research team made a definite MBI diagnosis after incorporating several sources of information that included extensive clinical assessments, cognitive, and neuropsychiatric testing.

4. RESEARCH STUDIES

4.1. STUDY 1

Mallo, S. C., Patten, S. B., Ismail, Z., Pereiro, A. X., Facal, D., Otero, C., & Juncos-Rabadán, O. (2020). Does the neuropsychiatric inventory predict progression from mild cognitive impairment to dementia? A systematic review and meta-analysis. *Ageing Research Reviews*, *58*, 101004. DOI: https://doi.org/10.1016/j.arr.2019.101004 (IF 2019= 10.61; Q1).

4.1.1. Background

The NPI and the NPI-Q are the most commonly used measures to assess ABS in clinical and research settings. Although both are specific to dementia populations, several studies have used these instruments to assess ABS in MCI. While some studies have concluded that ABS in MCI increased the risk of dementia, others did not. The objective of this systematic review and meta-analysis was to determine if NPI/NPI-Q scores predict conversion from MCI to dementia.

4.1.2. Method

Articles published between January 1999 and September 2018 were selected from PsycINFO, PubMed, SCOPUS, and Web of Science. Inclusion criteria were: 1) diagnosis of MCI at baseline following clinical criteria; 2) report NPI or NPI-Q total score in converters versus non-converts; 3) empirical longitudinal studies; and 4) concerned about the role of ABS as risk factors for conversion from MCI to dementia. Exclusion criteria were: 1) articles sampled or contained a majority of participants from a special population (e.g.: patients with cancer); and 2) inability to contact the authors requiring important information related to an article. Random effects models were used, and heterogeneity was explored with stratification and a random-effect-meta-regression. The overall conversion rate and the Standardized Mean Difference (SMD) for evolution, as a function of NPI/NPI-Q scores, were calculated.

4.1.3. Results

The overall conversion rate from MCI to dementia was 35%. Mean NPI/NPI-Q scores were higher in converters versus in non-converters, with the overall SMD (0.21, 95% CI-0.00, 0.42) approaching significance (z= 1.95, p=0.052). Heterogeneity was observed in studies of more than two years of follow-up and in a study with a mean age of more than 80 years. This heterogeneity concerned the size, not the direction of the difference.

4.1.4. Conclusions

These findings suggest that NPI/NPI-Q ratings are associated with conversion from MCI to dementia, significantly in studies with a > 2 years of follow-up and a mean age >80 years. The lack of sensitivity of the NPI-Q on the earliest ABS symptoms may explain why the overall SMD only approached significance. Additionally, the result may also be subject to a lack of specificity due to the transient symptom meeting the scoring threshold over the relatively short reference range of the NPI and NPI-Q.

4.2. STUDY 2

Mallo, S. C., Ismail, Z., Pereiro, A. X., Facal, D., Lojo-Seoane, C., Campos-Magdaleno, M., & Juncos-Rabadán, O. (2019). Assessing mild behavioral impairment with the mild behavioral impairment checklist in people with subjective cognitive decline. *International psychogeriatrics*, *31*(2), 231-239. DOI: https://doi.org/10.1017/S1041610218000698 (IF= 2.94; Q2).

4.2.1. Background

The relationships between subjective cognitive complaints, the core clinical criteria for SCD, and ABS have been explored in recent studies. These findings have suggested that the presence of ABS in people with SCD could be a risk factor for MCI and dementia. Further, recent studies have established the prevalence of MBI in people with SCD. However, they used only one MBI criterion among those established by the ISTAART-AA using a transformation algorithm of the NPI. The following study's objectives were to estimate the prevalence of MBI in SCD participants, determine the validity of the MBI-C administered by phone in a SCD sample.

4.2.2. Method

One hundred twenty-seven participants with SCD were recruited from primary care centers. They performed an extensive evaluation, including the QSMC, MMSE, CAMCOG-R, NPI-Q, GDS-15, the Lawton and Brody Index, and the MBI-C, which was administered to an informant by phone. We conducted descriptive, logistic regression, ROC curve, and bivariate correlations analyses.

4.2.3. Results

The results indicated an MBI prevalence of 5.8% in SCD using all the ISTAART-AA MBI diagnostic criteria. MBI-C total score was low and differentiated people with MBI at a cut-off of 8.5 (optimizing sensitivity and specificity). MBI-C total score correlated positively with NPI-Q, QSMC from the informant, and GDS-15.

4.2.4. Conclusions

To our knowledge, this is the first study of the MBI-C in a sample of SCD participants. These results suggest that the phone administration of the MBI-C is useful for detecting MBI in people with SCD. Previous population-based and clinical studies reported a higher prevalence of MBI in SCD participants. However, they used the NPI and NPI-Q, which require one-month symptoms as a reference frame in contrast with the MBI-C, which involves a six-month duration and explicit later-life onset of symptoms. The MBI-C detected subtle ABS that were correlated with the NPI-Q, depressive symptomatology, and memory performance perceived by the participants' relatives.

4.3. STUDY 3

Mallo, S. C., Ismail, Z., Pereiro, A. X., Facal, D., Lojo-Seoane, C., Campos-Magdaleno, M., & Juncos-Rabadan, O. (2018). Assessing mild behavioral impairment with the mild behavioral impairment-checklist in people with mild cognitive impairment. *Journal of Alzheimer's Disease*, *66*(1), 83-95. DOI: 10.3233/JAD-180131 (IF=3.517; Q2). https://content.iospress.com/articles/journal-of-alzheimers-disease/jad180131

4.3.1. Background

Literature has indicated that ABS are common in MCI and increase the likelihood of developing dementia. Previous studies in MCI participants have estimated an MBI prevalence of 85.3% in a clinical sample and 48.9% in a community sample. However, they used a transformation algorithm of the NPI score to capture MBI criterion one. The following study's objectives were to estimate the MBI prevalence, study the score distribution, and the validity of the MBI-C administered by phone in a MCI sample.

4.3.2. Method

One hundred eleven patients from primary care centers were evaluated with the QSMC, MMSE, Cambridge Cognitive Assessment-Revised, NPI-Q, GDS-15, Lawton and Brody Index, and the MBI-C, which was administered by phone to participants' informants. Descriptive, logistic regression, ROC curve, and bivariate correlations analyses were performed.

4.3.3. Results

The prevalence of MBI diagnosis was 14.2%. The total MBI-C score differentiated people with MBI at a cutoff-point of 6.5, optimizing sensitivity and specificity. MBI-C total score correlated positively with NPI-Q, QSMC, GDS-15, and Lawton and Brody Index. No correlations were found between objective cognitive measures (MMSE and CAMCOG-R) and the MBI-C.

4.3.4. Conclusions

The findings suggested that the total MBI-C score, obtained by phone administration, is sensitive for detecting MBI in people with MCI. Previous studies reported a higher prevalence of MBI in MCI participants, both in clinical and population-based settings. Nevertheless, they used the NPI and NPI-Q, which require one-month symptoms as a reference frame. In contrast, the MBI-C involves a six-month duration and explicit later-life onset of symptoms. The MBI-C scores indicated that MCI participants had subtle ABS that were correlated to their subjective memory complaints reported by informants, depressive symptoms, and negatively with IADL. MBI-C and objective cognitive measures did not significantly correlate supporting the hypothesis that, despite MCI and MBI can co-occur, they reflect different pre-dementia syndromes.

4.4. STUDY 4

Mallo, S. C., Valladares-Rodriguez, S., Facal, D., Lojo-Seoane, C., Fernández-Iglesias, M. J., & Pereiro, A. X. (2020). Neuropsychiatric symptoms as predictors of conversion from MCI to dementia: a machine learning approach. *International Psychogeriatrics*, *32*(3), 381-392. DOI: https://doi.org/10.1017/S1041610219001030 (IF 2019= 2.94; Q2).

4.4.1. Background

Although the literature has suggested that ABS may increase the risk of dementia in MCI, some inconsistencies persist. Depression has been the most common studied ABS and has been usually associated with an increased risk. New scientific disciplines based on ML have emerged in recent years that show its potential to support diagnostic or risk estimation. The objective of the present study was to use a ML approach to compare ABS symptoms in participants of a clinical longitudinal study who developed dementia and those who did not.

4.4.2. Methods

The sample was composed of 128 participants at baseline (78 cognitively unimpaired and 50 with MCI). Man Whitney U and ML analyses were conducted. Nine algorithms were evaluated using a 10-fold stratified validation procedure. Performance metrics (accuracy, recall, F-1 score, and Cohen's kappa) were computed for each algorithm, and graphic metrics (ROC and precision-recall curves) and features analysis were computed for the best-performing algorithm. The measurements included were: diagnosis at baseline, months from the baseline assessment until the 3rd follow-up or development of dementia, gender, age, CCI, NPI-Q individual items, NPI-Q total severity, and total stress score and GDS-15 total score.

4.4.3. Results

Thirty participants developed dementia, while 98 did not. Most of the participants who developed dementia were diagnosed at baseline with amnestic multidomain MCI. The Random Forest Plot model provided the metrics that best predicted conversion to dementia (e.g., accuracy=0.88, F1=0.67, and Cohen's kappa=0.63). The algorithm indicated the importance of the metrics in the following (decreasing) order: months from first assessment, age, the diagnostic group at baseline, total NPI-Q severity score, total NPI-Q stress score, and GDS-15 total score.

4.4.4. Conclusions

To the best of our knowledge, this is the first study that uses a ML approach to explore ABS's role in conversion from MCI to dementia. Some ABS proxies, including NPI-Q total severity score, NPI-Q total stress score, and GDS-15 total score, were deemed as the most important variables for predicting conversion, adding further support to the hypothesis that some ABS are associated with a higher risk of dementia in MCI.

5. DISCUSSION

This discussion will be organized among the four objectives of this dissertation, which are explicitly linked to the papers of this work:

1. To review and meta-analyze whether ABS, measured with the NPI/NPI-Q, could predict progression from MCI to dementia in participants diagnosed with MCI at baseline according to diagnostic criteria.
2. To study the prevalence of MBI and some psychometric properties of the phone-administered MBI-C applied to informants and to determine if this instrument is valid to assess ABS in SCD participants.
3. To study the prevalence of MBI and some psychometric properties of the phone-administered MBI-C applied to informants and to determine if this instrument is valid to assess ABS in MCI participants.
4. To determine if NPI-Q scores predict conversion to dementia in MCI participants using a ML approach.

5.1. REVIEW ON THE PREDICTIVE VALIDITY OF AFFECTIVE-BEHAVIORAL SYMPTOMS IN THE CONVERSION OF MCI TO DEMENTIA

We carried out a systematic review and a meta-analysis of the literature to determine whether baseline ABS, measured by the NPI or NPI-Q, could predict conversion from MCI to dementia in people diagnosed with MCI at baseline according to diagnostic criteria.

Our motivation for conducting the systematic review was the inconsistent nature of the prior literature, which may be due to the imprecision of individual studies and methodological differences.

Two studies were rated as having "good" quality, whereas nine were rated as "fair." Surprisingly, studies rated as having "good" quality had a lower conversion rate than those rated as "fair." One reason for these results may be that quality studies had less percentage of attrition because the selection of participants was carried out more rigorously. One might speculate that these participants are healthier than those from studies rated as having "fair" quality. Therefore, these participants may be more likely to continue in the study and less likely to convert to dementia. These results point to the need for a more rigorous selection of participants, by applying criteria such as clearly specified study population, established inclusion and exclusion criteria, and sample size justifications.

The overall conversion rate from MCI to all-cause dementia was 35 %. Other meta-analyses estimated similar conversion rates, for example, in Mitchell & Shiri-Feshki (2009) the proportion of conversion was 39.2% and in Hu et al. (2017) was 34%. MCI has been considered a highly complex diagnostic entity, with a heterogeneous transition between normal aging and MCI subtypes, including progression of symptoms (worsening) or no change (persistent MCI) or even improvement of symptoms (recovery) (Ávila-Villanueva et al., 2018; Facal et al., 2015, 2019; Petersen et al., 2018). Research is needed to determine which variables are decisive to predict conversion to dementia, reversion to normal aging, or stability of the MCI diagnosis. Several variables did not significantly affect the conversion proportion: age, percentage of women, education level, number of measurements, and MCI criteria. Nonetheless, the duration of the follow-up and the mean age of the sample did have a significant effect.

We focused our meta-analysis on ABS, measured with the NPI or NPI-Q, and their role as risk factors from MCI to dementia. Our results showed that mean NPI and NPI-Q ratings were higher in MCI participants who converted to dementia versus those who did not, despite that the overall SMD only approached significance. Various studies have concluded that ABS increase the risk of dementia in clinical and research settings (Connors et al., 2017; Cooper et al., 2015; David et al., 2016; Pink et al., 2015; Pocnet et al., 2015). A meta-analysis (Cooper et al., 2015) performed with five studies, all of them using the NPI/NPI-Q, concluded that ABS predicted conversion from any MCI to all-cause dementia. Our results are in accordance with these findings, the estimated effect sizes within all subgroups were in the direction of higher NPI/NPI-Q scores in converters versus non-converters, and the heterogeneity observed concerned the size, not the direction, of the difference.

Our meta-analysis was not entirely decisive in showing that mean NPI/NPI-Q ratings are higher in respondents with MCI who convert to dementia, but an overall SMD approached significance. However, there was considerable heterogeneity observed, and the effect was evident in studies having more than two years of follow-up and a single study with a mean age of more than 80 years in its study sample. Furthermore, the estimated effect sizes within all subgroups were in the direction of higher NPI/NPI-Q ratings in converters, such that the heterogeneity observed concerned the size, not the direction, of the difference. These results suggest that NPI/NPI-Q ratings are associated with conversion to dementia in people with MCI.

Regarding the length of follow-up, our findings indicate that studies with more than two years of follow-up had a higher conversion rate. Notably, the seven studies with more than two years of follow-up achieved a significant effect on heterogeneity. In another meta-analysis (Mitchell & Shiri-Feshki, 2009), studies of less than three years were not included, and they obtained a conversion rate of 39.2 %, slightly higher than ours (35 %). Previous researchers have pointed out the potential role of follow-up duration in the symptom's progression (Facal et al., 2015). Consistent with this, a recent study (Cui et al., 2011) concluded that predictive values for MCI participants who converted after 12 months are generally higher than for MCI participants that converted within 12 months. Thus, time could be an essential variable in ABS progression, as it is in cognitive symptoms evolution (Cui et al., 2011; Facal et al., 2015) .

Additionally, a significant effect was found in one study with a mean age of more than 80. Thus, the effect of ABS in conversion seems to be higher in studies with very-old participants. Previous research has outlined that age is a risk variable when predicting the evolution from MCI to dementia (Matthews et al., 2008). Thus, age may be a risk factor for cognitive impairment and behavioral impairment, especially in very old participants. Future studies are needed to explore the effects of age on ABS symptoms.

The NPI and the NPI-Q are specific to dementia (Ismail et al., 2017a). Therefore, our results may be related to the lack of sensitivity on the earliest ABS and a lack of specificity due to transient symptoms. The MBI-C was specially developed to assess sustained and impactful ABS in pre-dementia states. Our validation analysis with the MBI-C pointed out good psychometric properties and associations with cognitive decline, according to the results reported in recent studies (Creese et al., 2019a; Hu, 2019). Investigations with the MBI-C may provide valuable information about ABS's role in the preclinical phases.

Some limitations of this meta-analysis should be mentioned. We only included 11 studies, probably due to our inclusion and exclusion criteria. Further, any search strategy involves trade-offs between sensitivity and specificity, and we cannot exclude the possibility that we failed to

detect one or more relevant studies. Besides, despite having contacted several authors to provide us with data on total NPI/NPI-Q scores, we did not get a response. Hence, only one population-based study was included. Therefore, we could not study if the sample type was a significant source of heterogeneity. However, all participants, regardless of whether they came from a clinical or population-based sample, were diagnosed as MCI with the same clinical criteria, and consequently, had the same risk of dementia. Previous studies have suggested that clinical samples report a higher prevalence of ABS, probably reflecting differences in demographics, study settings, MCI diagnosis and behavioral instruments used (Apostolova & Cummings, 2008; Ismail et al., 2017b; Monastero et al., 2009).

5.2. PREVALENCE OF MBI AND PSYCHOMETRIC PROPERTIES OF THE MBI-C IN SCD PARTICIPANTS

This objective corresponds to study number two. The role of ABS in SCD has not been studied as frequently as in MCI and dementia (Sheikh et al., 2018). To our knowledge, this was the first study of the MBI-C in a sample of people with SCD. MBI-C was administered by phone interview. The phone validation is highly beneficial in dispersed populations, where the participants have difficulties traveling to the health centers, or when they are not able to attend due to health reasons or scheduling.

In our study, during our seven-month recruitment time frame, the point prevalence of MBI in people with SCD, according to ISTAART-AA diagnosis criteria, was 5.8%. Previous studies have estimated a much higher MBI prevalence in SCD of 43.1% in a community sample (Mortby, Ismail, & Anstey, 2018c) and 76.5% in clinical samples (Sheikh et al., 2018). Some reasons may explain why these prevalence estimates are higher. The NPI and NPI-Q, used in these studies, require one month of symptoms as the reference frame, whereas the MBI-C involves a more rigorous expectation of six-month symptom duration and explicit later-life onset of symptoms. With this more rigorous standard for ABS, the MBI-C minimizes the inclusion of transient and reactive states in case detection. Decreasing the likelihood of infections or other medical conditions, change in living situation or relationships, or medication adjustments and side effects contributing to ABS ascertainment likely results in fewer MBI false positives (Ismail et al., 2017a). These two studies may be prone to lack of specificity due to this short time frame, and a lack of sensitivity due to retrofitting NPI criteria into MBI domains. Hence, our diagnosis was made more strictly, incorporating all the four ISTAART-AA MBI criteria, resulting in a more accurate estimate of prevalence.

The MBI-C total scoring was a significant predictor of MBI diagnosis. The cut-off point of 8.5 correctly classified 99% of the SCD sample, differentiating people with and without an MBI diagnoses with a sensitivity of 100% and a specificity of 96.3%. Since the MBI-C was explicitly developed as a case ascertainment instrument for the ISTAART-AA MBI criteria, and structured to be consistent with the MBI domains, high sensitivity and specificity were expected.

MBI-C total scoring correlated significantly and positively with NPI-Q and GDS-15, showing the convergent validity of MBI-C to assess ABS. In agreement with a previous study, broad measures of ABS are related to SCD (Mewton et al., 2014). Studies (Geda et al., 2014; Liew, 2020) suggest that ABS in healthy participants increase the risk of developing MCI and dementia. The positive and significant correlation with the GDS-15 is also in concordance with recent studies that showed that depression was associated to SCD (Burmester et al., 2016; Chin,

Oh, Seo, & Na, 2014). All the same, this relationship may be limited to clinical samples, because the patients are already concerned about their performance.

No correlation was found between MBI-C and Lawton IADL. Importantly, criterion two of the MBI diagnosis assesses if the ABS produce minimal impairment in interpersonal relationships and other aspects of social functioning or ability to perform at the workplace (Ismail et al., 2016). Commonly, people with MCI have problems performing complex functional tasks that they used to perform in the past (Albert et al., 2011), in contrast to people with SCD (Jessen et al., 2014). However, in MBI diagnosis, these impairments in social, occupational, or interpersonal function must be related to changes in personality and behavior, not cognitive decline (Ismail et al., 2016). It is important to note that many patients from our study did not meet criterion two because ABS were not of sufficient severity to affect function. This requirement speaks to the clinical relevance of the MBI criteria, and increase specificity by excluding symptoms without functional impact, which may not be risk factors for MCI and dementia.

No correlation was found between the MBI-C and cognitive performance measured by the MMSE or the CAMCOG-R. Even though MCI and MBI can co-occur, some authors have suggested that they are different syndromes (cognitive and behavioral) and that both increase the likelihood of dementia (Ismail et al., 2016). The absence of correlation found in this investigation may suggest that MBI and MCI are two different entities, one reflecting the neurobehavioral axis, and the other reflecting the neurocognitive axis of predementia syndromes.

MBI-C scoring was correlated with QSMC scores from the informant but not with QSMC from the patient. Juncos-Rabadán et al. (2012) found that memory difficulties reported by the informant had a higher prognostic value predicting objective performance than those reported by the MCI participants themselves. Further work is required to establish this. It is important to note that subjective cognitive complaints (from the informant and/or the patients themselves) constitute a criterion for diagnosing MCI (Albert et al., 2011). Our findings highlight the importance of assessing ABS in people with SCD since they could be early markers of decline.

Some limitations of our study are about the cross-sectional design implemented for the validation of the MBI-C in SCD, since it was not possible to draw conclusions about changes in prevalence over time, nor risk factors for evolution to objective cognitive impairment.

Psychometric properties of then MBI-C are need to be determined in future studies with large and transcultural samples. As this study was performed with a primary care clinical sample, more research is required to determine if the results vary in community samples, since prior literature has concluded that ABS are more frequent in clinical versus community samples (Ismail et al., 2017b). Moreover, more research is needed to determine if the new MBI criteria can be used to assist the diagnostic process and if the MBI-C is a helpful instrument for the early identification of individuals at risk of cognitive impairment.

5.3. Prevalence of MBI and psychometric properties of the MBI-C in MCI participants

This objective corresponds to study three. To our knowledge, this was the first validation study of the MBI-C in a sample of people with MCI. The prevalence of MBI in our primary care MCI sample was 14.2%. Previous studies, using traditional ABS rating scales such as the NPI and the NPI-Q, indicated an ABS prevalence in MCI populations ranges from 35% to 85% (Apostolova & Cummings, 2008; Monastero et al., 2009).Using a transformation algorithm of the

NPI/NPI-Q score to capture criterion one of MBI, the prevalence estimated in two recent studies was 85.3% in a clinical sample (Sheikh et al., 2018) and 48.9% in a community sample (Mortby et al., 2018c). As it was mentioned before, these percentages are significantly higher than in our sample, possibly due to the short frame of 1 month required by the NPI and NPI-Q. Our results comparing the two NPI-Q versions (one and six months) show that the 6-month reference range is more rigorous. As in our previous study, our diagnosis was made incorporating all the four ISTAART-AA criteria and many of our patients did not meet criterion two, because ABS were not of sufficient severity to produce minimal impairment in interpersonal relationships, other aspects of social functioning or ability to perform in the workplace. This requirement speaks to the clinical relevance of the ISTAART-AA MBI criteria and may increase diagnostic specificity by excluding symptoms with no functional impact.

Besides, our findings suggest that the phone administration of the MBI-C is useful for detecting MBI in people with MCI. A cutoff point of 6.5 significantly classified people with MBI diagnoses with a sensitivity of 100% and a specificity of 78.20%.

Regarding convergent validity, the MBI-C total score showed a mean significant positive correlation with one-month NPI-Q, six-month NPI-Q, and GDS-15. Following these results, our analyses have shown that patients with MBI have significantly higher scores on the NPI-Q, GDS-15, and four of the five domains of the MBI-C (decreased motivation, affective dysregulation, impulse dyscontrol, and social inappropriateness), than patients without MBI. Depression is one of the most common symptoms in MCI, with a recent meta-analysis estimating prevalence at 32%, but being higher in clinical than in community samples (Ismail et al., 2017b). MBI-C correlation with the GDS-15 provides reassurance that depressive symptoms are captured with the MBI-C.

The MBI-C detected subtle ABS correlated with functional impairment, as measured by the Lawton and Brody IADL Index. This finding suggests that the emergence of ABS may be related to early functional impairment. This result is under criterion two of the MBI diagnosis (Ismail et al., 2016), which stipulates that ABS produce minimal impairment in interpersonal relationships, other aspects of social functioning, or ability to perform at the workplace. People with MCI have problems performing complex functional tasks that they used to perform in the past (Albert et al., 2011). As established before, in MBI, these impairments in social, occupational, or interpersonal functions must be related to changes in personality and behavior, not due to changes in cognition (Ismail et al., 2016). This result highlights the importance of an early assessment of functionality in people at risk of cognitive impairment. While the expectation that functional impairment is due to ABS, and that this increases diagnostic specificity, the converse argument also applies. It is possible that awaiting functional impairment may result in diagnostic delays, missing the mildest or earliest symptoms, and chances for early intervention and clinical trial enrollment (Mortby et al., 2018a).

The findings have indicated that patients with MBI have higher scores on QSMC from the informants than those without MBI. The significant positive correlation between MBI-C and subjective cognitive performance, measured by the QSMC, is relevant, taking into account that subjective cognitive complaints are an essential criterion for the diagnosis of MCI (Albert et al., 2011). These results highlight the importance of evaluating ABS in people with MCI because they may be early markers of cognitive impairment and, therefore, early indicators of dementia. No correlation was found between the MBI-C and QSMC from the patient. As stated above, memory difficulties reported by the informant can show higher prognostic value predicting

objective performance than those reported by the MCI participants themselves (Juncos-Rabadán et al., 2012). Further studies are needed to determine the relationship between subjective cognitive complaints and ABS, and which type of subjective cognitive complaints (reported by the patients themselves or by the informants) are more accurate. No correlation was found between the MBI-C and objective cognitive measures (CAMCOG-R and MMSE). As it was previously suggested, this result supports the notion that while MBI and MCI can co-occur, they reflect different pre-dementia syndromes (neurobehavioral and neurocognitive), and that MBI is not merely a function of cognitive impairment (Ismail et al., 2016).

All the results suggest that the Spanish version of the MBI-C is especially useful for detecting MBI in people with MCI. There are several implications of this finding.

5.4. NPI-Q SCORES AS PREDICTORS OF CONVERSION TO DEMENTIA IN MCI PARTICIPANTS

To our knowledge, this was the first study that used an ML approach to explore the role of ABS in conversion from MCI to dementia. The role of ABS in predicting conversion to dementia has traditionally been studied by regression analysis (Acosta et al., 2018; Mortby et al., 2017) and Cox proportional hazard models (Rosenberg et al., 2013), and we used ML analysis as an innovative research approach.

ML algorithms were used to compare a sample of 128 participants to predict the risk of dementia. The use of the innovative ML approach based on the application of ML algorithms to socio-demographic data, primary health status and, ABS proxies, enabled prediction of conversion to dementia with good precision and accuracy. The Random Forest Plot Classifier produced the best results in terms of accuracy —due to represent the percentage of correctly classified subjects between converters and non-converters— and Cohen's kappa (Lotte et al., 2007). This algorithm correctly predicted which participants would and would not develop dementia, with an accuracy rate of 86% ± .00 and precision of 89% ± .09 and Cohen's kappa of 63% ± .30. According to the individual values of the metrics used, precision was slightly higher than recall, which indicates that the true positive rate is slightly higher. The slightly low recall score of .71 (.28) may indicate a large number of false negatives in this sample. This result is possible, as progression from MCI to dementia occurs for reasons other than ABS, such as cognitive performance (Michaud, Su, Siahpush, & Murman, 2017). Hence, Cohen's kappa score was fairly low. However, in general, the results showed that the Random Forest Plot Classifier is a good model for predicting conversion to dementia in MCI. Moreover, the Random Forest model provides other intrinsic benefits: the ability to generate diagnostic knowledge and to explain decisions in an easy way for health professionals. Finally, the ML approach contributes to extract significant information from a given dataset; to explain decisions based on quality metrics; to reduce the number of features necessary to obtain a prediction; and finally, to give more knowledge about the role of ABS in conversion from MCI to dementia.

The variables were ranked according to their importance using the Random Forest Plot Classifier. For good prediction, the following were identified as the most important variables (in decreasing order): 1) Months from the first assessment; 2) Age; 3) Diagnostic group at baseline; 4) Total severity score on the NPI-Q; 5) Total stress score on the NPI-Q; and 6) GDS-15 total score.

Accordingly, two diagnostic variables (months from the first assessment and diagnostic group at baseline), chronological age, and three ABS proxies were deemed the most important for

predicting dementia. Individual items of the NPI-Q and comorbidity did not contribute as much predictive value to the model as the variables mentioned above.

In our study, global measures of ABS indicated a higher risk of conversion to dementia, with converters characterized by higher scores on the NPI-Q total severity than non-converters (Acosta et al., 2018; Forrester et al., 2016; Mortby et al., 2017; Rosenberg et al., 2013). Hence, the features analysis results indicated that the total severity score of the NPI-Q was one of the most essential variables in predicting dementia in our model. While many studies concluded that NPI and NPI-Q total severity score increase the risk of dementia (Banks et al., 2014; Mortby et al., 2017), others did not (Brodaty, Woodward, Boundy, Ames, & Balshaw, 2011). Our results support the hypothesis that high NPI-Q scores are associated with an increased risk of dementia. Importantly, NPI-Q is a scale developed for dementia populations (Kaufer et al., 2000).

Our results are consistent with previously reported findings, confirming that the conversion rate increases with time since diagnosis and age of the participants (Corrada et al., 2010). Time is also very relevant when predicting the risk of dementia, previous studies have demonstrated before the potential role of mean follow-up duration in conversion rates (Facal et al., 2015).

Considering depressive symptomatology, the GDS-15 played an essential role in classifying the risk of conversion to dementia. Depression is the most common behavioral symptom in MCI (Ismail & Mortby, 2017). Both depressive symptoms and depression diagnosis are associated with a higher risk of dementia (Gonzales et al., 2017; Singh-Manoux et al., 2017), especially AD (Gonzales et al., 2017). Individuals with depressive syndromes may represent a subgroup of MCI that is highly vulnerable to accelerated cognitive decline (Gonzales et al., 2017). The GDS-15 was more predictive of progression from MCI to dementia than the individual depression/dysphoria item of the NPI-Q. This individual item is a single measure that simply collects information such as whether patients are sad, suffering from low mood, or often crying (Kaufer et al., 2000), while the GDS-15 is a screening scale including 15 questions (Sheikh & Yesavage, 1986). The GDS-15 provides much more extensive information, which may explain why the ML analysis indicated that it significantly increased the risk of dementia while the individual item of the NPI-Q did not. The GDS-15 is a self-reported measure, while the individual item of the NPI-Q is informant-based. Therefore, the information may be qualitatively and significantly different (Sanchez-Villegas et al., 2008).

Apathy and anxiety played also an important role in predicting conversion and were the seventh and eighth most predictive ABS. Systematic reviews and meta-analysis did not conclude whether anxiety increases the risk of cognitive impairment. Some studies concluded that anxiety is a risk factor for dementia (Li & Li, 2018; Pietrzak et al., 2012) and AD (Mah, Binns, Steffens, & The Alzheimer's Disease Neuroimaging Initiative , 2015), while others provided mixed results (Cooper et al., 2015). Regarding apathy, recent research has suggested that apathy may be an independent risk factor for progression from MCI to dementia (Guercio, Donovan, Munro, & Aghjayan, 2015; Pink et al., 2015).

Some limitations should be acknowledged. The relatively new application of ML techniques in the fields of aging and neurocognitive disorders should be recognized. Nonetheless, the performance metrics obtained were adequate, and the algorithms used have been well tested in other similar areas. Further, the group who developed dementia had a shorter follow-up period than those who did not. Whatsoever, we included time as a predictor in the features' analysis to avoid bias, and the overlapping strategy has been suggested as a useful tool when there is variability in the time between the baseline and the follow-up assessment and the potential role of

time in the study of MCI as a set of transitional states. Thirdly, we used the NPI-Q scale, which, as previously mentioned, has several limitations. However, there are currently no validated and adapted instruments to assess ABS in pre-dementia states. Finally, our study did not include a diagnostic group of participants with SCD. Recent findings have suggested that subjective cognitive complaints increase the risk of MCI (Masters et al., 2015a) and dementia, especially AD (Gifford et al., 2014; Jessen et al., 2011; Mitchell et al., 2014; Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Nonetheless, SCD is a new diagnostic entity, and future studies should determine its predictive risk of cognitive impairment.

6. CONCLUSIONS

The present work was devoted to a better understanding of ABS as risk factors for conversion to dementia and to determine the prevalence and some psychometric properties of the MBI-C in a sample of participants in pre-dementia states. Form the results obtained in these studies it is concluded that:

1. NPI/NPI-Q total score was associated with conversion from MCI to dementia. This association achieved significance both in studies with a 2 or more years of follow-up and a mean age of over 80 years.
2. The phone administration of the MBI-C was valid for detecting MBI in people with SCD and MCI. Cutoff points for MBI of 6.5 and 8.5 in the MBI-C were, respectively, established for MCI and SCD.
3. The prevalence estimated for the MBI in participants recruited in primary health care centers with MCI and in SCD was, respectively, low (14.8%) and very low (5.2%).
4. Considering sociodemographic, health and ABS variables, ABS proxies, including NPI-Q total severity score, NPI-Q total stress score, and GDS-15 total score, were the more relevant variables in predicting conversion from MCI to dementia.

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8. APPENDIX

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APPENDIX 1: THE MILD BEHAVIORAL IMPAIRMENT CHECKLIST (MBI-C)

Mild Behavioral Impairment Checklist (MBI-C)

Date: _____

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3

Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?	Yes	No	1 2 3
Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?	Yes	No	1 2 3
Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?	Yes	No	1 2 3
Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?	Yes	No	1 2 3
Does the person no longer find food tasteful or enjoyable? Are they eating less?	Yes	No	1 2 3
Does the person hoard objects when she/he did not do so before?	Yes	No	1 2 3
Has the person developed simple repetitive behaviors or compulsions?	Yes	No	1 2 3
Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?	Yes	No	1 2 3
This domain describes following societal norms and having social graces, tact, and empathy			
Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others' feelings?	Yes	No	1 2 3
Has the person started talking openly about very personal or private matters not usually discussed in public?	Yes	No	1 2 3
Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?	Yes	No	1 2 3
Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?	Yes	No	1 2 3
Does the person now talk to strangers as if familiar, or intrude on their activities?	Yes	No	1 2 3
This domain describes strongly held beliefs and sensory experiences			
Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?	Yes	No	1 2 3
Has the person developed suspiciousness about the intentions or motives of other people?	Yes	No	1 2 3
Does she/he have unrealistic beliefs about her/his power, wealth or skills?	Yes	No	1 2 3
Does the person describe hearing voices or does she/he talk to imaginary people or "spirits"?	Yes	No	1 2 3
Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	Yes	No	1 2 3

APPENDIX 2: SPANISH VERSION OF THE MILD BEHAVIORAL IMPAIRMENT CHECKLIST (MBI-C)

Mild Behavioral Impairment Checklist (MBI-C)

Date: _____

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3

Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?	Yes	No	1 2 3
Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?	Yes	No	1 2 3
Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?	Yes	No	1 2 3
Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?	Yes	No	1 2 3
Does the person no longer find food tasteful or enjoyable? Are they eating less?	Yes	No	1 2 3
Does the person hoard objects when she/he did not do so before?	Yes	No	1 2 3
Has the person developed simple repetitive behaviors or compulsions?	Yes	No	1 2 3
Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?	Yes	No	1 2 3
This domain describes following societal norms and having social graces, tact, and empathy			
Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others' feelings?	Yes	No	1 2 3
Has the person started talking openly about very personal or private matters not usually discussed in public?	Yes	No	1 2 3
Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?	Yes	No	1 2 3
Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?	Yes	No	1 2 3
Does the person now talk to strangers as if familiar, or intrude on their activities?	Yes	No	1 2 3
This domain describes strongly held beliefs and sensory experiences			
Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?	Yes	No	1 2 3
Has the person developed suspiciousness about the intentions or motives of other people?	Yes	No	1 2 3
Does she/he have unrealistic beliefs about her/his power, wealth or skills?	Yes	No	1 2 3
Does the person describe hearing voices or does she/he talk to imaginary people or "spirits"?	Yes	No	1 2 3
Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	Yes	No	1 2 3

Arturo X. Pereiro Rozas, en calidade de director da tese doutoral realizada por Dª Sabela C. Mallo, doutoranda no PD Desenvolvemento psicolóxico, Aprendizaxe e Saúde informa que as contribucións da doutoranda ás publicacións presentadas son as seguintes:

Estudo 1:

Mallo, S. C., Patten, S. B., Ismail, Z., Pereiro, A. X., Facal, D., Otero, C., & Juncos-Rabadán, O. (2020). Does the neuropsychiatric inventory predict progression from mild cognitive impairment to dementia? A systematic review and meta-analysis. *Ageing Research Reviews*, *58*, 101004. DOI: https://doi.org/10.1016/j.arr.2019.101004 (IF 2019= 10.61; Q1).

O estudo, sendo o último en publicarse, foi o primeiro en deseñarse e iniciarse. A doutoranda participa no deseño do estudo, realiza a revisión e selección dos traballos que cumpren os criterios de busca e inclusión, participa na aplicación dos criterios PRISMA e nas análises de acordo interxuices, e finalmente asume o protagonismo principal na redacción do manuscrito.

Estudo 2:

Mallo, S. C., Ismail, Z., Pereiro, A. X., Facal, D., Lojo-Seoane, C., Campos-Magdaleno, M., & Juncos-Rabadán, O. (2019). Assessing mild behavioral impairment with the mild behavioral impairment checklist in people with subjective cognitive decline. *International psychogeriatrics*, *31*(2), 231-239. DOI: https://doi.org/10.1017/S1041610218000698 (IF= 2.94; Q2).

A doutoranda participa na adaptación do instrumento, está implicada no deseño do estudo e, sendo bolseira de investigación participa na recolida de datos do proxecto de investigación no que se enmarca o estudo, tamén participa na análise e interpretación dos datos, e finalmente asume o protagonismo principal na redacción do manuscrito.

Estudo 3:

Mallo, S. C., Ismail, Z., Pereiro, A. X., Facal, D., Lojo-Seoane, C., Campos-Magdaleno, M., & Juncos-Rabadan, O. (2018). Assessing mild behavioral impairment with the mild behavioral impairment-checklist in people with mild cognitive impairment. *Journal of Alzheimer's Disease*, *66*(1), 83-95. DOI: 10.3233/JAD-180131 (IF=3.517; Q2). https://content.iospress.com/articles/journal-of-alzheimers-disease/jad180131

Estudo realizado co mesmo instrumento empregado no estudo anterior e cun deseño semellante, no que participa activamente a doutoranda, tamén colabora na recolida de datos do proxecto de investigación no que se enmarca o estudo, e participa tanto na análise e interpretación dos datos como na redacción do manuscrito.

Estudo 4:

Mallo, S. C., Valladares-Rodriguez, S., Facal, D., Lojo-Seoane, C., Fernández-Iglesias, M. J., & Pereiro, A. X. (2020). Neuropsychiatric symptoms as predictors of conversion from MCI to dementia: a machine learning approach. *International Psychogeriatrics*, *32*(3), 381-392. DOI: https://doi.org/10.1017/S1041610219001030 (IF 2019= 2.94; Q2).

Estudo realizado con mostra do proxecto de investigación no que participa como bolseira a doutoranda en actividades de avaliación. Participa no deseño do estudo, na interpretación das análises de datos, e asume o protagonismo principal na redacción do manuscrito.

Arturo X. Pereiro Rozas, en calidade de director da tese doutoral realizada por Dª Sabela Mallo, doutoranda no PD Desenvolvemento psicolóxico, Aprendizaxe e Saúde informa que estas son as publicacións que achegan contidos á tese, con indicadores do factor de impacto (Impact Factor, IF) das revistas nas que se atopan no ano de publicación, e a posición relativa na categoría a que pertence (quartile, Q):

Estudo 1:

Mallo, S. C., Patten, S. B., Ismail, Z., Pereiro, A. X., Facal, D., Otero, C., & Juncos-Rabadán, O. (2020). Does the neuropsychiatric inventory predict progression from mild cognitive impairment to dementia? A systematic review and meta-analysis. *Ageing Research Reviews*, *58*, 101004. DOI: https://doi.org/10.1016/j.arr.2019.101004 (IF 2019= 10.61; Q1).

Estudo 2:

Mallo, S. C., Ismail, Z., Pereiro, A. X., Facal, D., Lojo-Seoane, C., Campos-Magdaleno, M., & Juncos-Rabadán, O. (2019). Assessing mild behavioral impairment with the mild behavioral impairment checklist in people with subjective cognitive decline. *International psychogeriatrics*, *31*(2), 231-239. DOI: https://doi.org/10.1017/S1041610218000698 (IF= 2.94; Q2).

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