**UNIVERSITE DE LAUSANNE- FACULTE DE BIOLOGIE ET MEDECINE**

Département de Psychiatrie - CHUV

Service Universitaire de Psychiatrie de l'Age Avancé

# La personnalité comme facteur prédictif des symptômes comportementaux et psychologiques chez les patients qui présentent des troubles cognitifs légers

**THESE**

préparé sous la direction du Prof. Armin von Gunten

et présentée à la Faculté de biologie et médecine de l'Université de Lausanne

pour l'obtention du grade de



**DOCTEUR EN MEDECINE**



par

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***La personnalité comme facteur prédictif de l'apparition de symptômes psychologiques et comportementaux chez les patients qui présentent des troubles cognitifs légers à l'âge avancé***

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*de la Faculté de Biologie et de Médecine*

*Madame le Professeur Stephanie Clarke*
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## Résumé

Cette thèse a eu pour objectif d'étudier l'impact des traits de la personnalité sur le développement de symptômes comportementaux et psychologiques (SCP) chez des personnes qui présentent de troubles cognitifs légers (Mild Cognitive Impairment ou MCI) par rapport à un groupe de sujets contrôle en bonne santé sans troubles cognitifs. Cette thèse s'est s'inscrite dans une étude plus large regroupant des aspects neuropsychologiques, génétiques et des marqueurs structuraux cérébraux d'imagerie chez les mêmes participants.

La découverte d'un MCI a un impact important en soulevant la question d'éventuels traitements préventifs et de modification du cours d'un trouble ou d'une maladie sous-jacente. Les manifestations cliniques, notamment les SCP, sont source de souffrance chez le patient et les proches et la première cause d'institutionnalisation. Connaître les liens entre la personnalité et les SCP chez les patients qui présentent un MCI s'avère primordial si l'on veut les détecter précocement et favoriser un traitement mieux adapté, tant pharmacologique que psychothérapeutique, pour tenter de freiner leur impact sur l'évolution de la maladie.

Nous avons comparé 52 patients MCI avec 83 sujets contrôles. La personnalité au moment de l'étude et estimée rétrospectivement à cinq ans en arrière a été évalué par un proche à l'aide du NEO-PI-R, principal instrument basé sur le Five Factor Model. Pour évaluer la présence de SCP nous avons utilisé l'inventaire neuropsychiatrique (NPI-Q). Les analyses ont étés contrôlées en tenant compte des principales variables confondantes.

Le groupe MCI présente des traits de personnalité prémorbide différents de ceux des participants contrôles avec des niveaux inférieurs d'ouverture à l'expérience, d'agréabilité et de conscience. Les changements de personnalité sont marqués chez les MCI avec une augmentation du névrosisme et une diminution de l'extraversion et de la conscience. La personnalité est restée stable chez le groupe contrôle. Le groupe MCI présente souvent des SCP, en particulier des symptômes affectifs (dépression, anxiété, irritabilité, troubles du sommeil) et de l'apathie tandis que les SCP sont presqu'inexistantes chez le groupe contrôle. Les valeurs de névrosisme plus élevés et l'ouverture à l'expérience plus basses sont associées à la présence de SCP. En plus, le changement de la personnalité, à savoir l'augmentation du névrosisme et la diminution de conscience sont associées à la présence de SCP, aux symptômes affectifs et à l'apathie. La diminution d'extraversion et d'ouverture à l'expérience sont associées à la présence de SCP, aux symptômes affectifs mais pas à l'apathie.

Cette étude montre que la personnalité change déjà au stade de MCI et que l'apparition des SCP affectifs et de l'apathie est précoce. Certains profils prémorbides et changements de personnalité sont associés à la présence de SCP. L'évaluation de ces changements peut favoriser le diagnostic précoce des troubles cognitifs. Des études prospectives sur des patients MCI sont essentielles afin d'approfondir la compréhension des facteurs de risque liés à la personnalité sur le déclin cognitif et les SCP associés.

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# Personality Traits and Behavioural and Psychological Symptoms in Patients with Mild Cognitive Impairment

**Keywords:** personality, mild cognitive impairment, old age, behavioural and psychological symptoms.

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**Short title: Personality and BPS in MCI**

**Abstract:**

**Background and Aims:** Both personality changes and behavioural and psychological symptoms (BPS) may be associated with mild cognitive impairment (MCI) in later life and help identify incipient dementia. We wished to investigate the links between personality and BPS in MCI. Method: We studied premorbid personality traits as estimated five years back and their changes in 83 control subjects and 52 MCI patients using the NEO-PI-R for the Five-Factor Model completed by a proxy. Information on BPS was obtained using the Neuropsychiatric Inventory (NPI). Analyses were controlled for current depression and anxiety.

**Results:** premorbid neuroticism and openness to experience were associated with the total NPI score. The changes in neuroticism, extraversion, openness to experiences, and conscientiousness were associated with apathy and affective symptoms.

**Conclusions:** Personality changes and BPS occur in MCI. The occurrence of affective BPS and apathy is associated with both premorbid personality and their changes.

## Introduction

Mild cognitive impairment (MCI) is both a clinically and etiologically heterogeneous condition with cognitive characteristics lying between normal aging and dementia and a possible precursor to dementia [1, 2, 3, 4, 5]. According to some authors, a little less than two thirds of MCI subjects developing dementia have Alzheimer's disease (AD) and about one third vascular dementias [3] while recent research both from clinical and population-based samples suggest that MCI patients have a high risk of progressing to a full dementia syndrome [3, 6]. Although a number of biological markers have been identified that further increase the risk of developing AD in these patients, their predictive value as to which patients are in the early phase of AD is still limited [6].

Behavioural and psychological symptoms (BPS) may accompany MCI and could be an early indicator of the presence of a dementia disorder [5, 7, 8, 9]. BPS include mood disorders (among others: depression, sleep disturbances or anxiety), psychotic symptoms (delusions, hallucinations), and a number of behavioural symptoms or signs such as euphoria, apathy, irritability, aberrant motor behaviour, disinhibition and eating disorders [7, 8, 10]. BPS occur in 50% to 80% of people with dementia in the course of the disease [7] and their prevalence in MCI ranges from 35% to 85% depending on the BPS type observed [8]. Data from recent systematic reviews suggest that anxiety, depression, apathy, agitation, and irritability are the most common BPS in MCI [4, 7, 8]. BPS in subjects with MCI are similar to those observed in AD [8]. Patients with BPS may present more rapid cognitive decline and earlier institutionalization and are likely to cause greater caregiver depression than those without BPS [7]. Similar to BPS, personality changes often occur during dementia [11, 12,

13], but personality characteristics are often not well defined. Among the different personality models, dimensional approaches of personality, such as the Five-Factor Model, assess personality traits independently of their normal or pathological significance and are well suited for studies not primarily focussing on personality pathology. However, changes of premorbid personality traits were evaluated in patients with cognitive decline [14, 15, 16, 17, 18, 19, 20]. Premorbid proneness to experience psychological distress has been related to the level of impairment in episodic memory in persons with AD [15]. Increased rigidity or egocentrism, growing apathy, and impaired emotional control have been described in patients developing dementia [16]. Agitation and passivity were more common in patients with memory changes who later progressed to AD [17]. Patients with AD have increased neuroticism and decreased extraversion, openness, conscientiousness, and agreeableness in relation to the normal elderly [11, 12, 13, 20, 21]. A number of studies suggest that higher levels of neuroticism could increase the risk of MCI while moderate extraversion might be a protective factor [22]. Other findings support that MCI subjects differ in their personality traits compared to healthy controls and that higher premorbid neuroticism increases the risk of developing MCI in patients with similar levels of formal education [23].

Premorbid personality may also favour BPS in later dementia [24, 25, 26, 27] but these links remain unclear, due among other reasons, to the often unclear personality concepts used in different studies. Studies have shown personality changes and BPS in early AD [11, 13], but these findings are preliminary and have not been replicated in MCI. Thus, the aim of this study was to investigate the relationship between premorbid personality traits or their changes and BPS in patients with MCI as compared to cognitively healthy subjects. We hypothesized that MCI subjects had different premorbid personality traits when compared to healthy controls. We expected higher levels of premorbid neuroticism and lower levels of premorbid extraversion, openness to experience, agreeableness and conscientiousness in MCI subjects compared to the control group [11, 12, 13]. Furthermore, we hypothesized that MCI subjects underwent a personality change characterized by an increase in neuroticism and a decrease in extraversion, openness and conscientiousness while personality traits would remain unchanged in normal controls [13, 18]. Finally, we hypothesized that premorbid personality traits and personality change in MCI patients would be associated with the occurrence of BPS [11, 13, 21, 24, 25, 26, 27].

## Materials and Methods

### Subjects

Fifty-two patients diagnosed with MCI according to Winblad et al. 2004 [3] were recruited within the geriatric and gerontopsychiatric structures of the university hospitals of Lausanne and Geneva. MCI subjects are neither normal nor demented as there is evidence of cognitive deterioration according

to subjective self or informant report in conjunction with objective cognitive deficits; activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired as a consequence of cognitive change [2, 3]. Cognitive impairment was defined depending on age and education (1= primary school certificate, 2= professional certificate, 3= higher school diploma or university degree). Both single and multiple domains MCI were included [2]. Eighty-three control subjects were recruited through word of mouth and by advertisements in magazines catering to the elderly.

**Procedure**

All patients had a comprehensive psychiatric, neuropsychological, and functional evaluation that was carried out by a psychiatrist and a neuropsychologist in training. Subjects had to be older than 55 years of age, speak French and be accompanied by a proxy. The proxies are all French-speaking; they all live with the participant or have very regular contact although we have not quantified this frequency. The proxy is mostly a family member, usually the spouse, child or else a long-term companion.

A cognitive assessment battery, including the Mini Mental status examination, *range 0-30* [28], was administrated. The Informant Questionnaire on Cognitive Decline IQCODE, *16 items ranging from 1 to 5* (Jorm, 1989) [29], Activity of Daily Living ADL, *range 0-6* (Katz, 1998) [30] and Instrumental of Activity Daily Living, IADL, *range 0–8* (Lawton and Brody, 1969) [31] were administered to investigate the baseline level of functional performance. The absence of dementia was defined according to ICD-10 criteria (WHO, Masson 1994) [32]. Healthy subjects were required to have a Clinical Dementia Rating *score of 0* (Morris, 1993) [33] and MCI subjects a *score of 0.5*. The Hospital Anxiety and Depression scale, *14 items ranging from 0 to 42*, *7 anxiety items ranging from 0 to 21*, *7 depression items ranging from 0 to 21* was also administered to control for current affective status (Zigmond and Snaith, 1983) [34]. Most subjects had a brain MRI and Apo-E genotyping. All subjects with a history of a major neurological disorder, current or past, alcohol or drug abuse or a major psychiatric disorder other than dysthymia or mild depression were excluded.

**Assessment of BPS**

To assess BPS the Neuropsychiatric Inventory (Kaufer DI et al., 2000) [10] was administered through an interview with a close proxy of each patient. This instrument is a recognized armamentarium to investigate BPS in cognitive disorders, including MCI. It allows the rating of 12 domains including delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, sleep disturbances, and eating disorders. Any of these symptoms is rated

on a *3-point severity scale*. The sum of the 12 individual domain scores yields the total NPI-score *(maximum 36)*.

**Personality assessment**

The NEO-PI-R (Revised NEO Personality Inventory, Costa and McCrae, 1992) [35] is a 240-item questionnaire based on the statistically derived five-factor model of personality rated on a five-point agreement scale. It is organized according to five personality traits (factors): neuroticism, extraversion, openness to experience, agreeableness and conscientiousness; each factor being subdivided into six facets.

The NEO-PI-R was given to and completed by a proxy to describe the study subject's personality at the moment of the study as well as retrospectively, considering personality as it was five years back. Following the formal acceptance of the research (protocol 85/08) by the local ethics committee written informed consent was obtained from all participants before inclusion in the study.

**Statistical analysis**

The data were analyzed using SPSS, Version 19 (SPSS INC, Chicago, IL) and R Development Core Team [36]. As appropriate, parametric and non-parametric descriptive statistics were used for demographic and clinical data. ANCOVA was used to compare premorbid personality characteristics and their changes between the MCI and control groups, adjusted for age, gender, and current depressive and anxiety symptoms. Logistic regression was performed to predict 'caseness' (MCI versus control) with age, gender, level of education and premorbid personality traits as predictors. Post-hoc analyses were carried out only in the clinical group. Poisson regression (general linear model) was used to examine possible associations between personality and the total score of BPS. As the scores for most NPI domains were not normally distributed, transformations were successfully applied and each abnormal NPI variable dichotomized. Associations between personality traits and common BPS found in the MCI group were performed using logistic regressions (binomial general linear model) adjusted for age, gender, and symptoms of depression and anxiety. The threshold was set arbitrarily at $p < 0.05$ for all analyses.

**Results**

Among the 135 participants, 52 individuals (33w, 19 m) were cognitively impaired and 83 (59 w, 24 m) were healthy control subjects. Gender distribution was similar, $\chi2(1)=0.85$, $p=0.355$, but MCI patients were significantly older than the control subjects. Education level was similar. As expected, the MCI group had lower scores than the control group on the MMS and IADL and higher scores on

the IQCODE scales. Groups did not differ as to ADL and the HAD scores (total HAD, HAD depression and HAD anxiety). 51 MCI subjects (98%) and 67 controls (80%) were examined for APO E4. The group did not differ as to the APO E4 (presence of allele on 39% of MCI and 37 % of controls;

$\chi2(5)=2.86$, $p=0.721$). Finally and for informational purposes, 88% of participants attended an MRI to exclude strokes or tumours.The subjects' characteristics are shown in Table 1.

**Table 1: Demographic and clinical characteristics of the study participants**

| | **MCI subjects (N=52)** | | **Healthy subjects (N=83)** | | | |
|---|---|---|---|---|---|---|
| | **Means** | **SD** | **Means** | **SD** | **T, χ2 or z statistics** | p value |
| Age | 70.04 | (SD=8.59) | 66.13 | (SD=7.18) | t(133)=-2.84 | p=0.005 |
| School level *Ranges 1-3* | 2.04 | (SD=0.62) | 2.22 | (SD=0.56) | t(133)= 1.71 | p=0.089 |
| HAD total *Range 0-42* | 8.37 | (SD=5.83) | 7.31 | (SD=4.68) | Z=-0.86 | p=0.386 |
| HAD depression *Range 0-21* | 3.13 | (SD=3.45) | 2.22 | (SD=2.19) | Z=-1.51 | p=0.129 |
| HAD anxiety *Range 0-21* | 5.23 | (SD=3.39) | 5.10 | (SD=3.09) | Z=-0.31 | p=0.753 |
| MMS *Range 0-30* | 28.19 | (SD=1.40) | 29.20 | (SD=1.03) | Z=-4.59 | p<0.001 |
| ADL *Range 0-6* | 5.85 | (SD=0.72) | 5.99 | (SD=0.11) | Z=-1.94 | p=0.052 |
| IADL *Range 0-8* | 7.62 | (SD=1.14) | 7.99 | (SD=0.11) | Z=-3.48 | p<0.001 |
| IQ CODE *Range 1-5* | 3.10 | (SD=0.63) | 2.92 | (SD=0.38) | Z=-2.80 | p= 0.005 |

Background characteristics presented as mean and standard deviations for controls and MCI patients.

HAD = Hospital anxiety and depression, HAD depression, HAD anxiety.MMS = Mini Mental State Examination.

ADL = Activity Dailing Living. IADL = Instrumental Activity Dailing. IQCODE = Informant Questionnaire of Cognitive Decline. T = student T test for independant samples. Z = non parametric U test of Mann-Whitney, absolute values.

**Personality profiles in patients with MCI as compared to healthy controls**

After controlling for age, gender, MMS score and the presence of symptoms of depression and anxiety to avoid the usual confounding factors, the personality characteristics, both premorbid and the changes of personality over five years, differed significantly between the MCI and healthy control subjects (cf. Table 2).

**Table 2: Premorbid personality traits and personality changes in healthy controls and MCI subjects**

| | MCI subjects (N=52) | | Healthy subjects (N=83) | | | |
|---|---|---|---|---|---|---|
| | | | **Premorbid personality** | | | |
| | **Means** | **SD** | **Means** | **SD** | **t statistic** | **p values** |
| Neuroticism | 84.26 | (SD=23.62) | 77.97 | (SD=20.88) | t=1.45 | p=0.148 |
| Extraversion | 101.01 | (SD=17.85) | 106.01 | (SD=17.44) | t=-0.78 | p=0.434 |
| Openness to experiences | 98.28 | (SD=16.15) | 108.45 | (SD=18.65) | t=-2.10 | p=0.037 |
| Agreeableness | 122.82 | (SD=20.48) | 132.15 | (SD=18.33) | t=-2.74 | p=0.007 |
| Conscientiousness | 120.63 | (SD=18.75) | 132.39 | (SD=19.09) | t=-3.26 | p=0.001 |
| | | | **Personality changes** | | | |
| Change of neuroticism | 5.26 | (SD=12.12) | 0.93 | (SD=5.82) | t=2.42 | p=0.017 |
| Change of extraversion | -4.32 | (SD=10.14) | -0.59 | (SD=4.31) | t=-2.87 | p=0.005 |
| Change of openness to experiences | -0.67 | (SD=3.51) | 0.22 | (SD=2.61) | t=-1.08 | p=0.279 |
| Change of agreeableness | -0.32 | (SD=5.16) | 0.38 | (SD=3.06) | t=-0.66 | p=0.506 |
| Change of conscientiousness | -5.11 | (SD=13.50) | -0.31 | (SD=3.63) | t=-2.34 | p=0.021 |

Personality traits and changes of personality, comparaison between controls and MCI subjects, adjusted by age, gender, MMS and current depression and anxiety (HAD). Values represented means and standard deviations (SD). T= t-test for independent samples.

The MCI group had higher premorbid neuroticism and lower premorbid extraversion scores than controls. These differences disappeared after adjustment for HAD scores. However, even after adjustment, significantly lower scores on openness, agreeableness and conscientiousness remained in the MCI group.

Changes in personality were marked in MCI subjects with increasing levels of neuroticism and decreasing levels of extraversion and conscientiousness. Openness to experience and agreeableness remained stable. In the healthy group, all personality patterns remained stable over time.

**Premorbid personality and the development of MCI**

We performed a logistic regression to investigate the relationship between premorbid personality traits and the development of MCI. The five personality traits were controlled for age, gender, and the level of education. Our analyses showed that subjects scoring higher on conscientiousness had a lower probability to be associated with MCI (cf. Table 3).

**Table 3: Predictors of MCI**

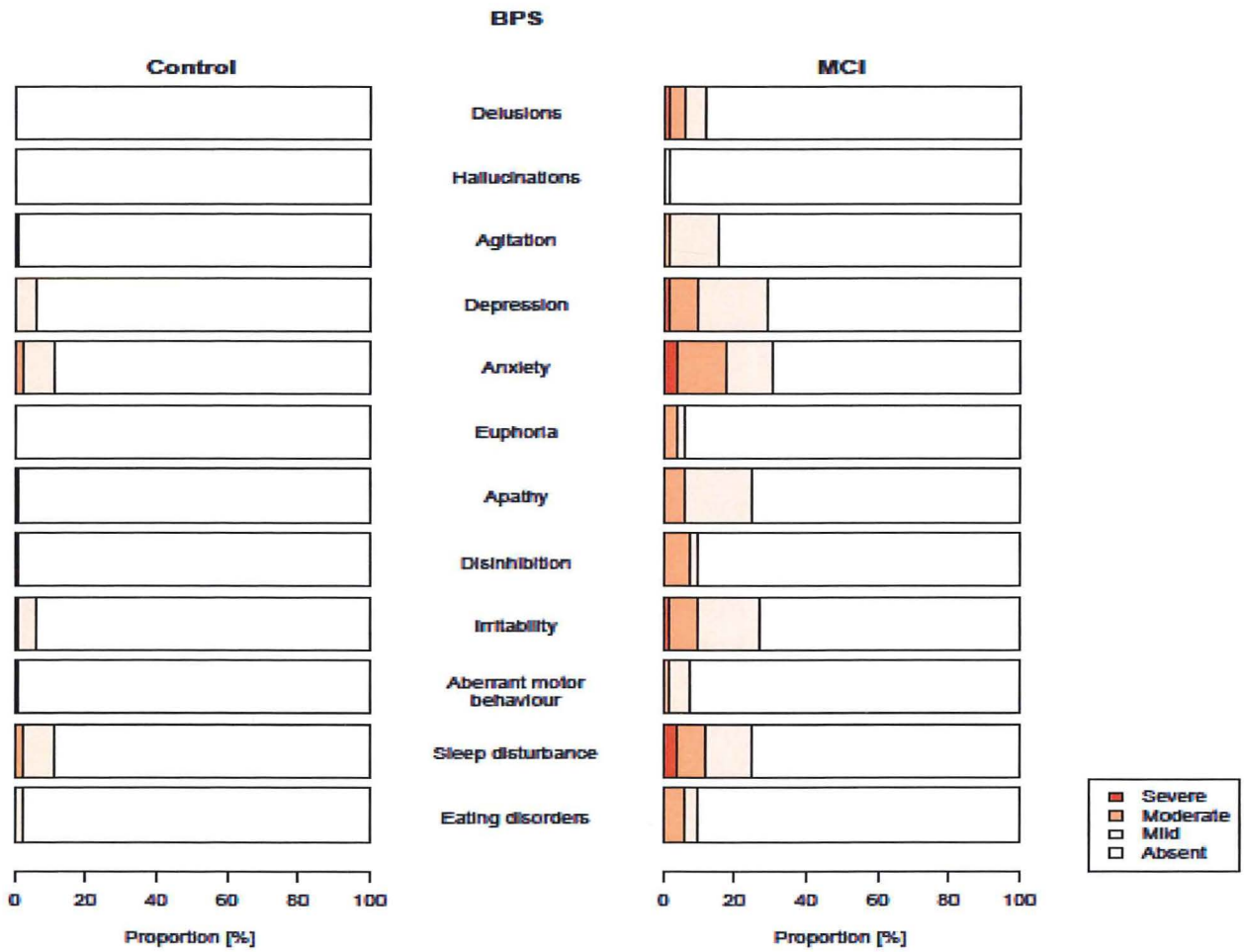
| | Coefficient B | Std Error | 95% CI | z value | Pr ( >\|z\| ) |
|---|---|---|---|---|---|
| **Variable** | | | | | |
| Gender | 0.060 | 0.507 | -1.05- 0.93 | 0.119 | 0.905 |
| Age | 0.067 | 0.028 | 0.01- 0.12 | 2.338 | 0.019 |
| Level Education | -0.323 | 0.372 | -1.05- 0.40 | -0.870 | 0.384 |
| Neuroticism | -0.006 | 0.011 | -0.02- 0.01 | -0.581 | 0.561 |
| Extraversion | -0.002 | 0.012 | -0.02- 0.02 | -0.164 | 0.869 |
| Openess to experience | -0.020 | 0.014 | -0.04- 0.00 | -1.428 | 0.153 |
| Agreeableness | -0.022 | 0.012 | -0.04- 0.00 | -1.781 | 0.075 |
| Conscientioussnes | -0.034 | 0.012 | -0-06- 0.01 | -2.759 | 0.006 |

Logistic regression was applied using the following variables: level of education, age, gender and the premorbid domains of personality to predict MCI 'caseness'.

**BPS in patients with MCI as compared to healthy controls**

BPS were very rarely reported in healthy subjects, the values being systematically higher in MCI patients. The most frequent BPS in MCI subjects were depression, anxiety, apathy, irritability and sleep disturbances (cf. Figure 1).

**Figure1: BPS in control (N= 83) and MCI (N=52) subjects (%)**




This graphic shows the differences of % in BPS between MCI and control subjects

The two groups differed significantly regarding: total NPI score (Z=-3.71, $p$<0.001), delusions (Z=-3.15, $p$=0.002), agitation (Z=-3.20, $p$=0.001), depression (Z=-3.70, $p$<0.001), anxiety (Z=-3.05, $p$=0.002), euphoria (Z=-2.20, $p$=0.002), apathy (Z=-4.40, $p$<0.001), disinhibition (Z=-2.32, $p$=0.020), irritability (Z=-3.42, $p$=0.001), and sleep disturbances (Z=-2.26, $p$=0.024).

**Relationship between BPS and premorbid personality as well as personality changes in the MCI group**

In the MCI group, premorbid neuroticism is positively and significantly associated with the total NPI scores and premorbid openness to experience is negatively correlated. The total NPI score is also positively correlated with the changes of personality over time, in particular, increased neuroticism and decreased extraversion, openness to experience and conscientiousness.

Depression, anxiety, irritability and sleep disorders were predicted by increasing levels of neuroticism and decreasing levels in extraversion and conscientiousness. Apathy was associated positively with increasing neuroticism and decreasing conscientiousness. Anxiety and irritability were associated with decreasing levels in openness to experience. Premorbid openness to experience was associated negatively with anxiety, apathy and sleep disorders. No association was found between BPS and premorbid agreeableness, extraversion, and conscientiousness (cf. Table 4).

**Table 4: Relation between personality domains and BPS in MCI subjects**

| | | BPS | | | | |
|---|---|---|---|---|---|---|
| | *Total NPI-Q* | *Depression* | *Anxiety* | *Apathy* | *Irritability* | *Sleep disturbances* |
| ***Premorbid Personality Traits*** | | | | | | |
| Premorbid Neuroticism | **χ2(1)=4.01 p=0.045** | χ2(1)=1.36 p=0.243 | χ2(1)=3.32 p=0.068 | χ2(1)=2.38 p=0.122 | χ2(1)=1.08 p=0.297 | χ2(1)=1.95 p=0.162 |
| Premorbid Extraversion | χ2(1)=1.44 p=0.229 | χ2(1)=0.24 p=0.623 | χ2(1)=0.98 p=0.321 | χ2(1)=3.15 p=0.076 | χ2(1)=0.81 p=0.368 | χ2(1)=0.06 p=0.803 |
| Premorbid Openness to experiences | **χ2(1)=6.12 p=0.013** | χ2(1)=2.63 p=0.105 | **χ2(1)=5.50 p=0.019** | **χ2(1)=4.34 p=0.037** | χ2(1)=2.91 p=0.088 | **χ2(1)=4.99 p=0.025** |
| Premorbid agreeableness | χ2(1)=2.55 p=0.110 | χ2(1)=0.80 p =0.368 | χ2(1)=0.67 p=0.411 | χ2(1)=0.33 p=0.563 | χ2(1)=0.02 p=0.888 | χ2(1)=2.22 p=0.136 |
| Premorbid Conscientiousness | χ2(1)=1.44 p=0.229 | χ2(1)=0.64 p=0.420 | χ2(1)=1.21 p=0.271 | χ2(1)=0.22 p=0.635 | χ2(1)= 3.41 p=0.065 | χ2(1)=0.00 p=0.999 |
| ***Changes in personality traits*** | | | | | | |
| Neuroticism changes | **χ2(1)=10.68 p=0.001** | **χ2(1)=5.97 p=0.015** | **χ2(1)=8.46 p=0.004** | **χ2(1)=7.14 p=0.008** | **χ2(1)=7.87 p=0.005** | **χ2(1)=6.72 p=0.010** |
| Extraversion changes | **χ2(1)=5.70 p=0.017** | **χ2(1)=4.07 p=0.015** | **χ2(1)=4.34 p=0.037** | χ2(1)=2.81 p=0.094 | **χ2(1)=4.17 p=0.041** | **χ2(1)=5.31 p=0.021** |
| Openness to experiences changes | **χ2(1)=5.77 p=0.016** | χ2(1)=0.08 p=0.767 | **χ2(1)=5.29 p=0.021** | χ2(1)=3.30 p=0.069 | **χ2(1)=4.36 p=0.037** | χ2(1)=3.35 p=0.067 |
| Agreeableness changes | χ2(1)=1.45 p=0.227 | χ2(1)=1.17 p=0.279 | χ2(1)=0.76 p=0.382 | χ2(1)=1.92 p=0.165 | χ2(1)=0.74 p=0.389 | χ2(1)=1.75 p=0.185 |
| Conscientiousness changes | **χ2(1)=7.11 p=0.008** | **χ2(1)=3.81 p=0.051** | **χ2(1)=7.44 p=0.006** | **χ2(1)=6.41 p=0.011** | **χ2(1)=8.10 p=0.004** | **χ2(1)=7.40 p=0.006** |

This table shows both premorbid personality and personality changes - adjusted for age, gender, as well as depression and anxiety symptoms - as predictors of neuropsychiatric symptoms. Statistics used: Poisson regression (general linear model) for total NPI, logistic regression for anxiety, depression, apathy, irritability and sleep disorders. Wald Chi square and p values significant at the 5% level are in bold.

## Discussion

This study shows that personality changes occur in MCI along with BPS, in particular affective disorders and apathy. The MCI group had lower levels of premorbid agreeableness, openness to experience and conscientiousness, whilst neuroticism increased and extraversion and conscientiousness decreased over time. Changes in neuroticism, extraversion, openness to experience and conscientiousness were associated with BPS while only premorbid neuroticism and openness to experience were associated with BPS.

The hypothesis that premorbid personality traits may be related with cognitive decline was confirmed by a number of previous studies [13, 14, 15, 17, 22, 23, 34]. Proneness to psychological distress measured by items of the neuroticism scale of the NEO-FFI was associated with a higher risk of AD independely of pathological markers of AD, a finding suggesting that in these patients less AD pathology might be needed to reach the clinical threshold of dementia [19]. Data from a recent publication showed that higher premorbid neuroticism was associated with an increased risk of developing MCI [23]. Other findings supported a strong relationship between cognitive ability in early life and cognitive function and AD in later life and these conditions were considered more important than lifestyle or environmental risk factors [39].

In general, the authors suggest an intricate situation as a combination of risk factors rather than a single factor is likely to predict cognitive decline in these patients. Neuroticism, extraversion and conscientiousness are the personality domains implicated in these studies [11, 12, 20, 22, 23]. In our study, only lower levels of premorbid conscientiousness were associated with MCI, but groups differed in openness to experience, agreeableness and conscientiousness. This points out that there are differences in premorbid personality traits as well as personality changes even after adjusting for age, gender, the level of education and HAD score between MCI subjects and control subjects in that premorbid conscientiousness was associated with MCI. This partially supports other published data reporting patients diagnosed with a memory disorder to score significantly higher on premorbid neuroticism and lower on openness to experience, extraversion, and conscientiousness [21], although short of statistical significance, the trend is similar in our MCI sample.

Personality changes occur in our MCI patients but, as expected, not in control subjects. The level of neuroticism increases, whilst those of extraversion and conscientiousness decrease. Our findings are consistent with previous findings as this pattern of personality traits is observed in patients who suffer from AD [11, 12, 13, 20, 21] and, even more in focus with this study, in patients with MCI ; in these studies, an increase in negative emotion and a decrease in extraversion were reported [17]. Agreeableness seems to be the most stable personality domain over time in both MCI patients and in

patients who develop dementia [11, 12]. Thus, significant personality changes follow a specific trend in patients with AD [11, 12] and, as it were, in MCI subjects, an observation that contrasts with the stability of personality observed in healthy subjects [11, 12]. Finally, these results show that personality changes can occur very early in the disease process [11, 12, 13], at least, at the MCI stage.

BPS were quite frequent in our clinical sample which is in keeping with the findings of a number of previous studies [4, 7, 8, 10]. BPS in MCI display a similar pattern compared to AD [8]. We find a high prevalence of affective symptoms and apathy similar to other investigations [4, 5, 7, 8, 9].

A number of studies suggest that premorbid personality characteristics may be predictive of BPS in dementia [20, 24, 25, 26, 27] while still others reach the opposite conclusion for patients at an early stage of AD [13, 40, 41]. Some of these characteristics may correspond to an over expression of premorbid personality traits [11, 13, 21], but no such studies are available for MCI. Our study shows an association between premorbid personality traits and BPS. These findings argue for the hypothesis that premorbid personality may in part explain the later occurrence of BPS in MCI. Thus, in our MCI sample, only premorbid neuroticism and openness to experience were associated with the total NPI score and premorbid openness to experience with anxiety, apathy, and sleep disturbances. This result is supported by previous research that established links between openness to experiences and affective disorders [25]. However, the design of our study does not allow ascertaining a direct link between premorbid personality and BPS in MCI which would need a prospective study design.

As for premorbid personality, few studies dealt with the possible link between personality changes and BPS. In our MCI patients, personality changes significantly and these changes are associated with BPS. Personality changes in four domains (neuroticism, extraversion, openness to experience, and conscientiousness) were associated with the overall BPS score. All four domains were associated with anxiety and irritability while changes in neuroticism, extraversion, and conscientiousness were associated with depression and sleep disorders. Apathy was associated with changes in neuroticism and conscientiousness. Previous studies have established the links between personality, especially neuroticism and depression in early AD patients [20] and our research in MCI subjects are consistent with these studies. However, interpreting these results deserves caution. Thus, some authors observed that personality changes may be accompanied by BPS while premorbid personality traits did not predict BPS [13, 37, 40, 41]. This suggests a diachronic relationship between personality changes and BPS in early AD. However, the development in parallel of BPS and personality changes may not be entirely interdependent [13]. Indeed, our results show that personality changes in MCI follow a predictable pattern similar to that observed in AD while the occurrence of BPS seems to be

less predictable and temporally more unstable than personality changes [13]. Furthermore, personality changes could be more directly related to biological changes in the brain while BPS may be better understood as multi-etiologically explained intercurrences [13, 42]. Longitudinal studies will shed light on these complex interplays [13].

Several limitations of this study should be acknowledged. First, the small sample size did not allow separating the MCI group into different subtypes. Second, due to the clinical setting of this study, selection bias could overestimate the frequency of some personality traits as well as BPS which we found in our MCI group. Finally, assessment of personality traits was based on proxy ratings as opposed to self reports and this could have introduced some bias given the various filters through which the heterogeneous group of proxies may have described personality traits.
The inclusion of a healthy group and the strict exclusion of psychiatric and neurological co-morbidities give validity to the results. The broad definition of MCI is similar to the reality of clinical settings and may be seen as a positive strength of the study.

**Conclusion**

As both personality changes and BPS occur early in the course of the dementias, their assessment may favour early diagnosis of cognitive disorders. Both prospective studies in healthy subjects and follow-up studies on MCI samples would further our understanding of personality-related risk factors for cognitive decline and the links between non-cognitive and cognitive signs and symptoms in the various cognitive disorders in the elderly. Furthermore, caring for patients with dysfunctional personality traits and associated BPS might be a means of slowing the evolution of cognitive disorders, as well as reducing patient and carer distress.

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