A comparison of neurocognitive decline in older adults in same-sex and opposite-sex relationships.

Riccardo Manca[a], Annalena Venneri[a]

[a] Department of Neuroscience, University of Sheffield, Sheffield, UK

Corresponding author:
Professor Annalena Venneri
Department of Neuroscience, University of Sheffield, Beech Hill Road, Sheffield, South Yorkshire, S10 2RX, UK
Email: a.venneri@sheffield.ac.uk
Tel: +44 114 271 3430
Fax: +44 (0) 114 271 3158

Acknowledgements

The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P30 AG062428-01 (PI James Leverenz, MD) P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P30 AG062421-01 (PI Bradley Hyman, MD, PhD), P30 AG062422-01 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P30 AG062429-01(PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P30 AG062715-01 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

This is a summary of independent research carried out at the NIHR Sheffield Biomedical Research Centre (Translational Neuroscience). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. RM is funded by a grant from Neurocare to AV.

Abstract

Background: Individuals from sexual minorities experience health inequalities that have detrimental impacts on their health, especially in the elderly, by exacerbating care needs and symptoms of chronic conditions such as Alzheimer's disease (AD). Neurocognitive decline due to AD in the sexual minority population remains under-investigated. However, being in a relationship may mitigate the risk of experiencing cognitive impairment.

Objective: The aim of this study was to investigate whether cognitive decline and brain atrophy may differ in people from sexual minorities.

Methods: Clinical data for this study were selected from the National Alzheimer's Coordinating Center's Uniform Data Set and structural MRI data collected across 14 Alzheimer's Disease Centers. Eighty participants were included: 20 patients with AD and 20 healthy controls (HC) in same-sex relationships were identified and matched to groups of participants (20 AD and 20 HC) in opposite-sex relationships. The effects of diagnosis and relationship were investigated on all measures.

Results: No diagnosis-by-relationship interactions were found on any variable. However, *post hoc* analyses revealed that the opposite-sex group had grey matter atrophy mainly in medio-temporal areas, while in the same-sex group atrophy also extended to pre-frontal and cingulate areas. Severity of neuropsychiatric symptoms correlated with volume of pre-frontal and insular/temporal areas only in the same-sex group.

Conclusion: Neurocognitive decline due to AD may express similarly across individuals, independently of relationship type, thus suggesting a protective role of relational status. However, the same-sex group appeared to be more likely to experience at least one neuropsychiatric symptom and to have atrophy extending to fronto-limbic areas.

Keywords: Alzheimer's disease; neurodegeneration; marital relationship; sexual minorities; neuropsychiatric symptoms; cognition

1. Introduction

People belonging to sexual and gender minorities, i.e. people identifying as lesbian, gay, bisexual, transgender and other minorities (LGBT+), are more likely to face health inequalities than heterosexual people. This has been especially observed in the context of chronic diseases leading to greater detrimental effects as well as higher mortality rates (1). For example, cardiovascular risk factors are significantly more frequent in LGBT+ than in heterosexual people, especially among lesbian women (2), and this increased risk appears to be related mainly to exposure to early life adverse experiences (3). However, only very recently the first attempts have been made to set road-maps to investigate how health inequalities may exert long-lasting effects, particularly relevant for LGBT+ older adults (4). Despite the extensive literature on the LGBT+ youth, less attention has been dedicated to the ageing population. Indeed, the risk and the impact of dementia among sexual minorities are still largely overlooked issues (5, 6).

The last Alzheimer's Association Report mentioned social isolation as the main challenge for older LGBT+ people (7), who in general appear to have higher risk of life-time depression despite reporting better self-rated health (8). Qualitative investigations into the needs and the socio-legal issues faced by older adults from sexual minorities living with dementia showed that the relationship with their families and care-givers is crucial to determine patients' willingness to disclose their sexual orientation in healthcare settings and, hence, have access to appropriate care plans (9-11).

Neurocognitive functioning in the LGBT+ ageing population has rarely been investigated, probably due to the widespread lack of systematic collection of data on sexual orientation and gender identity in healthcare services (4). Recently, a cross-sectional population-based investigation carried out in the United States observed that people from sexual and gender minorities above 45 years of age were not more likely to report subjective cognitive decline compared to heterosexual people (12). However, non-white ethno-racial background and history of depression have been significantly associated with higher likelihood for LGBT+ older adults to present with subjective cognitive complaints (13). Moreover, a study found that the risk of mild cognitive impairment (MCI) and dementia appears to be similar between people in same-sex and opposite-sex relationships, thus suggesting that being in a relationship may be a protective factor against cognitive decline in individuals from sexual and gender minorities (14).

Currently, to the best of our knowledge, no findings have been published yet on whether neurodegeneration and cognitive and functional decline express similarly between heterosexual and non-heterosexual older adults.

Therefore, the present study aimed at comparing cognitive functioning, neuropsychiatric symptoms and patterns of neurodegeneration between people in same-sex and opposite-sex relationships.

2. Methods

2.1. Database description

The sample of individuals included in this study was selected by consulting the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), i.e. a standardized database of clinical data collected by a number of NIA-funded Alzheimer's Disease Centers (ADCs) in the United States (15, 16). Each center received approval for data collection by its own institutional review board prior to submitting data to NACC. All ADCs obtained informed consent from participants recruited. Participants were also asked to identify a study partner they were in contact with regularly to answer questions about the participants' health status. No additional ethical approval was required locally since the NACC database includes data that are anonymized and publicly available for download upon request.

2.2. Sample selection

Participants with UDS data collected between September 2005 and August 2019 were screened. A selection procedure analogous to another study (14) was followed to identify individuals from sexual minorities by comparing the sex reported by each participant and his/her spouse/partner, if presenting as the study partner. Where more than one visit was available, individuals were considered either in a same-sex or opposite-sex relationship if they reported such status consistently throughout the different assessment visits. Therefore, sexual orientation (heterosexual vs non-heterosexual) of participants included in this study was implied by their relationship status (opposite-sex vs same-sex).

The following inclusion criteria were used: 1) availability of a T1-weighted magnetic resonance imaging (MRI) scan taken +/-3 months from a UDS visit; 2) either normal cognition at all UDS visits or a primary clinical diagnosis of mild cognitive impairment/dementia due to AD at the UDS visit closest to the MRI scan; 3) availability of a study partner identified as a spouse/partner of the same sex of the study participant at any assessment visits. As a results, forty-one participants in same-sex relationships were identified: 21 healthy people and 20 patients with MCI/dementia due to AD. After quality-check of structural MRI data, one healthy participant had to be discarded because of the low quality of available data. Additionally, two groups of individuals (20 healthy and 20 MCI/AD) in an opposite-sex relationship were selected to be matched to those in

a same-sex relationship by sex, age, years of education, global cognitive functioning status, diagnosis, and APOE status.

2.3. Neuropsychological and clinical assessment

UDS data are collected by trained clinicians and clinic personnel from participants and their study partners about demographics, medical history, clinical examinations, functional and behavioral assessments, dementia severity, and a comprehensive neuropsychological evaluation. The diagnostic process varies across ADCs and a final clinical diagnosis is reached by either a team or a single physician who conducted the examination. Criteria initially used to diagnose MCI (17) and dementia due to AD (18) were updated in Version 3 of the UDS (19-21). Severity of dementia was measured by means of the CDR® Dementia Staging Instrument global score (22). The neuropsychological assessment protocol evolved and was updated in Version 3 of the UDS by replacing some of the cognitive tests (23, 24). For this reason, a selection of tests available for most participants included was made as follows (see Appendix A for details on test availability): Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) (MoCA scores were converted into MMSE scores following published norms (25) to allow comparison across all participants); Semantic Fluency Test (average of total correct items in two categories: animals and vegetables), Trail Making Test (part A, part B and difference B-A), Logical Memory Test (immediate and delayed recall), Digit Span Test (forward and backward recall). Additionally, the presence of neuropsychiatric symptoms was recorded by means of the Neuropsychiatric Inventory Questionnaire (NPI-Q) (26) and the Geriatric Depression Scale (GDS) (27).

2.4. APOE genetic profile

Biomarker data at NACC are best described as a convenience sample that is voluntarily submitted by individual ADCs. In general, no submission deadlines for data collection periods are defined for biomarker data. APOE genotype investigation is carried out independently by each ADC and by the Alzheimer's Disease Genetics Consortium (ADGC) and the National Institute of Aging Genetics of Alzheimer's Disease Data Storage Site (NCRAD) and later reported to NACC. If there is disagreement between the genetic profiling results submitted by the ADC and those submitted by the ADGC, the APOE genotype is considered as missing.

2.5. MRI parameters and pre-processing

MRI data collected as part of the NACC imaging database are also best defined as a convenience sample of images that are voluntarily submitted by each single ADC to NACC. Collection and acquisition protocols are variable across ADCs and may include different MRI scans. The focus of this study was on gray matter (GM) neurodegeneration and, thus, only structural T1-weighted MRI data collected in 14 ADCs were included in our analyses. Specifications about acquisition parameters and scanner characteristics are reported in Appendix B.

In consideration of the limited sample size of the groups selected according to our inclusion criteria, a decision was made to pool together scans acquired at different magnetic field strengths (19 at 1.5T and 61 at 3T). This represents a common practice as part of the increasing number of initiatives aimed at sharing neuroimaging data acquired on different MRI scanners across multiple sites across the world, such as the NACC and the Alzheimer's Disease Neuroimaging Initiative (ADNI) databases. Indeed, it has been shown that acquisition of structural MRI brain images of healthy people and patients with AD acquired on the same platform, but with different scanners and using different acquisition parameters, has significantly smaller effects than those of the disease itself (28). Moreover, although the combined analysis of structural images acquired at different MR field strengths may have a significant effect on the volumetric assessment of the cerebellum, the precentral gyrus and the thalamus bilaterally, no interaction was observed with disease status, i.e. findings about AD-related atrophy appear to be replicable and reliably detectable independently of the MR field strength in analysis of pooled structural MRI data (29). Consistently, Schmitter et al. (30) found very similar results regarding the classification of patients with MCI and dementia due to AD using two alternative datasets of T1-weighted images: either all acquired at 1.5T or when mixing images acquired at 1.5T and 3T.

All T1-weighted images were pre-processed using a standard voxel-based morphometry procedure (31). First, scans were segmented in order to obtain three tissue maps: GM, white matter (WM) and cerebrospinal fluid (CSF). Second, GM tissue maps were corrected for magnetic field inhomogeneities (32). Third, bias-corrected images were normalized to the standard ICBM template in the MNI space. Fourth, normalized GM maps were smoothed by applying an isotropic Gaussian kernel of 8 mm. All voxel-based morphometry pre-processing and analysis steps were carried out in SPM12 (Wellcome Centre for Human Neuroimaging, London, UK - https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running on Matlab R2016b (The Mathworks, Natick, Massachusetts, USA). The volume of the segmented tissue maps in milliliters was extracted for all participants using the SPM function *get_totals*. In order to account for variability in the MRI acquisition parameters, for

each participant a GM fraction was calculated as the proportion of GM volume divided by the total intracranial volume (sum of the GM, WM and CSF volumes).

2.6. Statistical analysis

All statistical analyses on clinical variables were carried out in SPSS version 26 (IBM, Chicago, IL, USA). Interactions between diagnosis (healthy vs MCI/AD) and relationship (same-sex vs opposite-sex) on both clinical ($p < 0.05$) and structural MRI ($p < 0.05$ FWE) measures were investigated using a 2x2 ANCOVA with age as a covariate, since it was the only variable differing between patients and healthy participants. Sex was also included in the model due to the unbalanced sex distributions in the study sample that could potentially bias the results. Finally, MRI field strength was also added as a covariate in MRI analysis since scanners of different field strength have been used across ADCs. Sub-group analyses were carried out limitedly to those participants with known APOE genotype in order to prevent biased findings due to a possible unbalanced distribution of APOE genotypes.

Additional *post hoc* analyses were carried out to ascertain potential differences in clinical profile, cognitive performance, and GM volume between patients and healthy participants in the same-sex and opposite-sex groups separately. Moreover, the volume of the GM clusters significantly smaller in patients compared to healthy participants in a same-sex relationship was extracted, divided by the total intracranial volume, and partial correlations between these volume ratios and NPI scores, using age as covariate, were investigated.

3. Results

3.1. Clinical and cognitive results

A total of 80 participants, 40 healthy controls and 40 patients with MCI/AD, were included in this study. Participants in same-sex and opposite-sex relationships, both patients and controls, were matched for all clinical and cognitive characteristics (Table 1). Compared to healthy controls, patients were older (years of age: 57.93 ± 11.14 vs 72.47 ± 10.18), had less GM overall, presented with worse cognitive performance on all tests and had higher NPI-Q scores (Table 2). Marginal differences were also noted in sex (20 males and 20 females among patients, but 29 males and 11 females among controls) and APOE genotype distributions that, however, depended on subjects' availability in the NACC database. No differences in racial composition were found between either patients or relationship groups, with the vast majority of participants reporting a white racial background.

- Insert Table **1** about here -

No diagnosis-by-relationship interaction effect was detected for scores on either the neuropsychological tests, the NPI-Q or the GDS. Indeed, patients in opposite-sex and same-sex relationships showed similar profiles of cognitive decline when investigated separately across all tests apart from the Digit Span Test, and patients in same-sex relationships also showed significantly lower scores on the Digit Span Test – backward ($F = 5.36$, $p = 0.03$) (Appendix C). In fact, no differences were observed in either CDR or cognitive test scores between patients in different relationships (Table 1). Moreover, although both groups of patients were significantly more likely than healthy controls to present with at least one neuropsychiatric symptom, this was highly significant in the same-sex group ($\chi^2 = 13.48$, $p < 0.001$), but only marginally in the opposite-sex group ($\chi^2 = 5.01$, $p = 0.02$). Instead, no differences in the rates of use of psychiatric medications were found between different relational groups (Appendix D). All of these results were replicated also when analyses were restricted only to participants with known APOE status.

- Insert Table **2** about here -

3.2. VBM results

The samples of participants in same-sex and opposite-sex relationships were matched for the proportion of brain images acquired at either 1.5T or 3T ($\chi2 = 0.069$, $p = 0.793$): nine 1.5T and thirty-one 3T images for the opposite-sex group, ten 1.5T and thirty 3T images for the same-sex group. Within the two relational groups, MRI field strengths were also equally distributed between the two diagnostic groups: $\chi2 = 3.58$, $p = 0.058$ for the OS group and $\chi2 = 2.13$, $p = 0.144$ for the SS group.

VBM analysis of T1-weighted scans revealed no relationship-by-diagnosis interaction effect as well as lack of a main effect of relationship type on regional GM volumes. Instead, diffuse GM loss was observed in the overall comparison between patients with MCI/dementia due to AD and healthy controls bilaterally in the temporal lobe, insula, posterior cingulate, occipito-temporal and medial prefrontal cortices (Table 3). However, the analyses carried out on participants in different relationship groups separately revealed different patterns of atrophy: patients in opposite-sex relationships showed mainly atrophy in the medial temporal lobe (MTL) bilaterally and the right insula/ superior temporal gyrus (STG); while the same-sex group had atrophy in the left

medial temporal lobe, the left insula/STG, medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) bilaterally (Figure 1; Table 2). The results survived also when participants with unknown APOE genotype were excluded from the analysis.

Volume ratios were calculated for four clusters of significantly greater GM atrophy in patients compared to healthy controls in same-sex relationships: the left MTL, the left insula/STG, the PCC and the mPFC bilaterally (Table 2). Overall, NPI scores were negatively correlated with volumes of two seeds: the left insula/STG ($\rho = -0.32$, $p < 0.01$) and the mPFC ($\rho = -0.34$, $p < 0.01$). NPI scores were not correlated with volume ratios of any seeds when participants were divided by diagnosis. However, when analyses were carried out on the overall sample, divided by relationship type, the pattern of associations was different: in the opposite-sex group, no significant negative correlations were detected for any of the seeds; while in the same-sex group NPI scores were correlated negatively with both the left insula/STG ($\rho = -0.41$, $p = 0.01$) and the mPFC volume ratios ($\rho = -0.42$, $p = 0.01$). No significant associations between regional GM volumes and GDS scores were observed.

- Insert **Figure 1** and **Table 2** about here -

4. Discussion

In this study we found that diagnosis of cognitive impairment due to AD does not interact with type of relationship in determining profiles of cognitive decline, neuropsychiatric symptoms, and neurodegeneration. However, when people in either opposite-sex or same-sex relationships were analyzed separately, different patterns of GM atrophy were detected in the comparison between patients and healthy controls. In fact, participants in a same-sex relationship had more pronounced GM atrophy in pre-frontal and posterior cingulate areas that was not observed for patients in the opposite-sex group. All significant findings survived after restricting the analyses only to those participants with known APOE genotype.

The same-sex group of patients was also far more likely to experience at least one neuropsychiatric symptom than healthy controls, while for the opposite-sex group this finding was only weakly significant. The higher propensity of the same-sex group to experience neuropsychiatric symptoms, although the total NPI and GDS scores were similar to those of the opposite-sex group, may account for the different patterns of atrophy. Indeed, the NPI score correlated with the volume of the left insula/STG and bilateral mPFC clusters only in the same-sex group, but not in the opposite-sex group. Interestingly, an association between atrophy in these areas and the presence of multiple neuropsychiatric symptoms in patients with AD has been previously observed, especially in

frontal areas (33-35). Consistently, functional connectivity alterations in fronto-parietal areas (36, 37) and metabolic dysfunction in limbic areas have also been linked to the emergence of neuropsychiatric symptoms across different stages of AD (38, 39).

Providing an explanation to account for a trend towards higher prevalence of neuropsychiatric symptoms in the same-sex group of patients is out of the scope of our investigations. Nonetheless, it must be noted that factors other than AD-related core neuropathological processes may independently contribute to the emergence of neuropsychiatric symptoms in this clinical population, such as genetic and environmental factors (35, 40). In the present study, we matched participants for APOE genotype since the ε4 allele has been suggested to represent a risk factor not only for AD itself, but also for neuropsychiatric symptoms, although current evidence is still inconsistent (41, 42). Moreover, no differences in rates of psychiatric medications, that might affect regional GM volumes, were found between relational groups. Therefore, we may suggest that environmental factors, probably related to personal history, might have played a role in determining different sub-threshold trajectories of GM degeneration between the opposite-sex and same-sex groups of patients in relation to neuropsychiatric manifestations. These findings emerged only when comparing patients with controls within relational groups either because of the small sample size or because these differences are very subtle and, therefore, are overshadowed by the main AD-related neuropathological changes when comparing the two patient groups directly.

Currently, the main theoretical framework used to explain ageing trajectories (43) and worse cognitive outcomes (44) in non-heterosexual compared to heterosexual older adults is minority stress. Minority stress is a theoretical construct to describe a stressful social environment experienced by people belonging to stigmatized minority groups, that in the case of sexual minorities it is thought to involve: experience of discrimination, expectation of discrimination based on sexual orientation, internalization of the stigma brought about by society, and concealment of sexual orientation (45). A flourishing literature has previously shown how minority stress in LGBT+ people has detrimental effects on both mental (46) and physical health (47), and can also lead to alterations in gene expression (48). For these reasons, minority stress is hypothesized to disrupt behavior and biological processes that, in turn, may impact cognitive functioning (49). Moreover, chronic stress and stress-related disorders have also been found to affect a variety of brain areas, particularly prefrontal and orbitofrontal cortices, as well as temporal and cingulate areas (50-52). Therefore, higher levels of stress experienced as a consequence of discrimination may be affecting individuals from sexual minorities and predispose them to higher rates of frontal and limbic atrophy and, in turn, higher rates of neuropsychiatric symptoms within the

context of a neurodegenerative condition. In fact, we found negative correlations between NPI scores and volumes of mPFC and left insula/STG, areas involved in emotional, behavioral and interoceptive processing. The lack of significant results in the direct comparison between relationship groups may be imputed mainly to the small sample size of the groups of participants: a factor that, however, depended on participants' availability in the NACC database. However, all participants included in our study were selected among those in a relationship with a partner/spouse. As mentioned above, LGBT+ older adults are at higher risk of social isolation and, therefore, our sample may represent a very specific sub-group within the wider LGBT+ elderly population. Interestingly, marital status seems to decrease the risk of dementia for people in a relationship (53, 54), and even to contribute to better treatment response (55). A possible explanation is that being in a long-term relationship represents a protective factor against minority stress and consequently reduces loneliness, i.e. perceived social isolation, and its negative consequences in LGBT+ elderly (56). Indeed, a variety of studies have reported that loneliness and social isolation may be independently associated with worse cognitive decline, particularly in memory functions (57-59), and with increased risk of AD (60, 61). These findings have also been corroborated by animal models of AD that have shown worse neural and behavioral outcomes as a consequence of social isolation (62). Recently, the first study to investigate the impact of social isolation on the brain of older adults found that experience of social isolation correlated negatively with GM volume in areas of the left MTL that are crucially involved in emotion processing and memory functions and particularly affected by AD pathology (63). It appears plausible, therefore, that being in a long-term relationship, either opposite-sex or same-sex, may mitigate the negative impact of either environmental (e.g. minority stress and social isolation) or biological (e.g. AD pathology) factors on cognitive functioning in line with the findings by Perales-Puchalt et al. (14). This may occur because long-term relationships offer the conditions to sustain optimal levels of social engagement, which is considered a fundamental aspect contributing to cognitive reserve (64) by attenuating the impact of neurodegeneration on cognitive performance (65).

A first limitation of this study is the identification of participants belonging to sexual minorities based on their relationship status, similarly to the procedure followed by Perales-Puchalt et al. (14). Although this approach has been previously used, we cannot exclude a potential selection bias. Indeed, due to the lack of data on sexual orientation as part of the NACC USD, non-heterosexual orientation (either homosexual or bisexual) was assumed for people in same-sex relationships, but we could not rule out that some participants in the opposite-sex group might have concealed their sexual orientation, a main issue in research on LGBT+ older adults (66). Second, individuals who were not in a relationship or did not have their partner/spouse as study partner were

excluded because it was not possible to infer their sexual orientation. This had two consequences: generation of groups with a small sample size and lack of a control group of non-heterosexual individuals not in a relationship, thus limiting the generalizability of our findings to the whole LGBT+ elderly population affected by AD and the interpretation of the potentially protective role of marital status. Third, the high variability in MRI acquisition protocols across ADCs warrants caution in interpreting and generalizing our VBM findings. However, it must be highlighted that the results we found were consistent with the pattern of atrophy expected from a comparison between patient with AD and healthy controls. Indeed, structural MRI data from the NACC database have already been used in multi-database studies to quantify whole-brain changes in ageing (67) and WM hyper-intensities (68), yielding results consistent across publicly available databases. Additionally, MRI magnetic field strength was added as a covariate in the VBM analyses as one of the main parameters that may affect image resolution. Moreover, we corrected all GM volumes extracted by dividing them by the total intracranial volume, thus minimizing any potential global volumetric differences due to discrepancies in MRI acquisition parameters.

5. Conclusion

Our preliminary findings suggest that people with AD from sexual minorities may experience more neuropsychiatric symptoms associated to GM atrophy mainly in pre-frontal areas, additional to AD-related MTL degeneration. Further prospective investigations in larger samples are needed to ascertain this trend and the inclusion of people without a partner/spouse would be beneficial to test whether being in a relationship may represent a protective factor against AD pathology and symptoms associated with it for LGBT+ elderly. Considering the complete lack of data, targeted investigations are also needed to investigate aging and dementia in transgender people. Findings already established on ethno-racial minorities with dementia (69) may provide a fruitful foundation of knowledge to translate into a new research line about the investigation of sexual (and gender) minority stress as a risk factor for cognitive decline within the wider framework of the dynamic bio-psycho-social model (70).

Conflict of interest

The authors report no conflict of interest.

References

1. Bristowe K, Hodson M, Wee B, Almack K, Johnson K, Daveson BA, et al. Recommendations to reduce inequalities for LGBT people facing advanced illness: ACCESSCare national qualitative interview study. Palliat Med. 2018;32(1):23-35.

2. Caceres BA, Brody A, Luscombe RE, Primiano JE, Marusca P, Sitts EM, et al. A systematic review of cardiovascular disease in sexual minorities. Am J Public Health. 2017;107(4):e13-21.

3. Hatzenbuehler ML, Slopen N, McLaughlin KA. Stressful life events, sexual orientation, and cardiometabolic risk among young adults in the United States. Health Psychol. 2014;33(10):1185-94.

4. Westwood S, Willis P, Fish J, Hafford-Letchfield T, Semlyen J, King A, et al. Older LGBT+ health inequalities in the UK: setting a research agenda. J Epidemiol Community Health. 2020.

5. McGovern J. The forgotten: dementia and the aging LGBT community. J Gerontol Soc Work. 2014;57(8):845-57.

6. Rosendale N, Josephson SA. The importance of lesbian, gay, bisexual, and transgender health in neurology: what's in a name? JAMA Neurol. 2015;72(8):855-6.

7. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. Alzheimers Dement. 2019;15(3):321-87.

8. Nelson CL, Andel R. Does sexual orientation relate to health and well-being? Analysis of adults 50+ years of age. Gerontologist. 2020.

9. Barrett C, Crameri P, Lambourne S, Latham JR, Whyte C. Understanding the experiences and needs of lesbian, gay, bisexual and trans Australians living with dementia, and their partners. Australas J Ageing. 2015;34 Suppl 2:34-8.

10. Fredriksen-Goldsen KI, Jen S, Bryan AEB, Goldsen J. Cognitive impairment, Alzheimer's disease, and other dementias in the lives of lesbian, gay, bisexual and transgender (LGBT) older adults and their caregivers: needs and competencies. J Appl Gerontol. 2018;37(5):545-69.

11. Peel E, Taylor H, Harding R. Sociolegal and practice implications of caring for LGBT people with dementia. Nurs Older People. 2016;28(10):26-30.

12. Brown MJ, Patterson R. Subjective cognitive decline among sexual and gender minorities: results from a U.S. population-based sample. J Alzheimers Dis. 2020;73(2):477-87.

13. Flatt JD, Johnson JK, Karpiak SE, Seidel L, Larson B, Brennan-Ing M. Correlates of subjective cognitive decline in lesbian, gay, bisexual, and transgender older adults. J Alzheimers Dis. 2018;64(1):91-102.

14. Perales-Puchalt J, Gauthreaux K, Flatt J, Teylan MA, Resendez J, Kukull WA, et al. Risk of dementia and mild cognitive impairment among older adults in same-sex relationships. Int J Geriatr Psychiatry. 2019;34(6):828-35.

15. Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. Alzheimer Dis Assoc Disord. 2007;21(3):249-58.

16. Besser L, Kukull W, Knopman DS, Chui H, Galasko D, Weintraub S, et al. Version 3 of the National Alzheimer's Coordinating Center's Uniform Data Set. Alzheimer Dis Assoc Disord. 2018;32(4):351-8.

17. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56(3):303-8.

18. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-44.

19. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270-9.

20. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-9.

21. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92.

22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412-4.

23. Morris JC, Weintraub S, Chui HC, Cummings J, Decarli C, Ferris S, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006;20(4):210-6.

24. Weintraub S, Besser L, Dodge HH, Teylan M, Ferris S, Goldstein FC, et al. Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). Alzheimer Dis Assoc Disord. 2018;32(1):10-7.

25. Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE. Comparative accuracies of two common screening instruments for the classification of Alzheimer's disease, mild cognitive impairment and healthy aging. Alzheimers Dement. 2013;9(5):529-37.

26. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12(2):233-9.

27. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol J Aging Ment Heal. 1986;5(1-2):165-73.

28. Stonnington CM, Tan G, Klöppel S, Chu C, Draganski B, Jack CR, Jr., et al. Interpreting scan data acquired from multiple scanners: a study with Alzheimer's disease. Neuroimage. 2008;39(3):1180-5.

29. Marchewka A, Kherif F, Krueger G, Grabowska A, Frackowiak R, Draganski B. Influence of magnetic field strength and image registration strategy on voxel-based morphometry in a study of Alzheimer's disease. Hum Brain Mapp. 2014;35(5):1865-74.

30. Schmitter D, Roche A, Maréchal B, Ribes D, Abdulkadir A, Bach-Cuadra M, et al. An evaluation of volume-based morphometry for prediction of mild cognitive impairment and Alzheimer's disease. Neuroimage Clin. 2015;7:7-17.

31. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000;11(6 Pt 1):805-21.

32. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26(3):839-51.

33. Boublay N, Schott AM, Krolak-Salmon P. Neuroimaging correlates of neuropsychiatric symptoms in Alzheimer's disease: a review of 20 years of research. Eur J Neurol. 2016;23(10):1500-9.

34. Boublay N, Bouet R, Dorey JM, Padovan C, Makaroff Z, Federico D, et al. Brain volume predicts behavioral and psychological symptoms in Alzheimer's disease. J Alzheimers Dis. 2020;73(4):1343-53.

35. Poulin SP, Bergeron D, Dickerson BC. Risk factors, neuroanatomical correlates, and outcome of neuropsychiatric symptoms in Alzheimer's disease. J Alzheimers Dis. 2017;60(2):483-93.

36. Munro CE, Donovan NJ, Guercio BJ, Wigman SE, Schultz AP, Amariglio RE, et al. Neuropsychiatric symptoms and functional connectivity in mild cognitive impairment. J Alzheimers Dis. 2015;46(3):727-35.

37. Wang X, Ren P, Mapstone M, Conwell Y, Porsteinsson AP, Foxe JJ, et al. Identify a shared neural circuit linking multiple neuropsychiatric symptoms with Alzheimer's pathology. Brain Imaging Behav. 2019;13(1):53-64.

38. Ballarini B, Iaccarino L, Magnani G, Nagehan A, Miller BL, Jagust WJ, et al. Neuropsychiatric subsyndromes and brain metabolic network dysfunctions in early onset Alzheimer's disease. Hum Brain Mapp. 2016;37(12):4234-47.

39. Ng KP, Pascoal TA, Mathotaarachchi S, Chung CO, Benedet AL, Shin M, et al. Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease. Neurology. 2017;88(19):1814-21.

40. Showraki A, Murari G, Ismail Z, Barfett JJ, Fornazzari L, Munoz DG, et al. Cerebrospinal fluid correlates of neuropsychiatric symptoms in patients with Alzheimer's disease/mild cognitive impairment: a systematic review. J Alzheimers Dis. 2019;71(2):477-501.

41. Christie D, Shofer J, Millard SP, Li E, Demichele-Sweet MA, Weamer EA, et al. Genetic association between APOE*4 and neuropsychiatric symptoms in patients with probable Alzheimer's disease is dependent on the psychosis phenotype. Behav Brain Funct. 2012;8:62.

42. D'Onofrio G, Panza F, Seripa D, Sancarlo D, Paris F, Cascavilla L, et al. The APOE polymorphism in Alzheimer's disease patients with neuropsychiatric symptoms and syndromes. Int J Geriatr Psychiatry. 2011;26(10):1062-70.

43. Fabbre VD, Jen S, Fredriksen-Goldsen K. The state of theory in LGBTQ aging: implications for gerontological scholarship. Res Aging. 2019;41(5):495-518.

44. Correro IL AN, Nielson KA. A review of minority stress as a risk factor for cognitive decline in lesbian, gay, bisexual, and transgender (LGBT) elders. J Gay Lesbian Ment Health. 2019;24(1):2-19.

45. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull. 2003;129(5):674-97.

46. Bostwick WB, Boyd CJ, Hughes TL, West BT, McCabe SE. Discrimination and mental health among lesbian, gay, and bisexual adults in the United States. Am J Orthopsychiatry. 2014;84(1):35-45.

47. Lick DJ, Durso LE, Johnson KL. Minority stress and physical health among sexual minorities. Perspect Psychol Sci. 2013;8(5):521-48.

48. Flentje A, Kober KM, Carrico AW, Neilands TB, Flowers E, Heck NC, et al. Minority stress and leukocyte gene expression in sexual minority men living with treated HIV infection. Brain Behav Immun. 2018;70:335-45.

49. Forrester SN, Gallo JJ, Whitfield KE, Thorpe RJ. A framework of minority stress: from physiological manifestations to cognitive outcomes. Gerontologist. 2019;59(6):1017-23.

50. Gianaros PJ, Jennings JR, Sheu LK, Greer PJ, Kuller LH, Matthews KA. Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. Neuroimage. 2007;35(2):795-803.

51. Guo P, Wang S, Chen C, Tian H, Li J, Zheng W, et al. Aberrant brain grey matter volume patterns differ among Chinese Han drug-naïve depression patients with acute and chronic stress. Oncotarget. 2017;8(54):91958-64.

52. Holmes SE, Scheinost D, DellaGioia N, Davis MT, Matuskey D, Pietrzak RH, et al. Cerebellar and prefrontal cortical alterations in PTSD: structural and functional evidence. Chronic Stress. 2018;2:2470547018786390.

53. Helmer C, Damon D, Letenneur L, Fabrigoule C, Barberger-Gateau P, Lafont S, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology. 1999;53(9):1953-8.

54. Sundström A, Westerlund O, Mousavi-Nasab H, Adolfsson R, Nilsson LG. The relationship between marital and parental status and the risk of dementia. Int Psychogeriatr. 2014;26(5):749-57.

55. Gallucci M, Spagnolo P, Aricò M, Grossi E. Predictors of response to cholinesterase inhibitors treatment of Alzheimer's disease: date mining from the TREDEM registry. J Alzheimers Dis. 2016;50(4):969-79.

56. Kuyper L, Fokkema T. Loneliness among older lesbian, gay, and bisexual adults: the role of minority stress. Arch Sex Behav. 2010;39(5):1171-80.

57. Lara E, Caballero FF, Rico-Uribe LA, Olaya B, Haro JM, Ayuso-Mateos JL, et al. Are loneliness and social isolation associated with cognitive decline? Int J Geriatr Psychiatry. 2019;34(11):1613-22.

58. Shankar A, Hamer M, McMunn A, Steptoe A. Social isolation and loneliness: relationships with cognitive function during 4 years of follow-up in the English Longitudinal Study of Ageing. Psychosom Med. 2013;75(2):161-70.

59. Tilvis RS, Kähönen-Väre MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. J Gerontol A Biol Sci Med Sci. 2004;59(3):268-74.

60. Rafnsson SB, Orrell M, d'Orsi E, Hogervorst E, Steptoe A. Loneliness, social integration, and incident dementia over 6 years: prospective findings from the English Longitudinal Study of Ageing. J Gerontol B Psychol Sci Soc Sci. 2020;75(1):114-24.

61. Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry. 2007;64(2):234-40.

62. Hsiao YH, Chang CH, Gean PW. Impact of social relationships on Alzheimer's memory impairment: mechanistic studies. J Biomed Sci. 2018;25(1):3.

63. Düzel S, Drewelies J, Gerstorf D, Demuth I, Steinhagen-Thiessen E, Lindenberger U, et al. Structural brain correlates of loneliness among older adults. Sci Rep. 2019;9.

64. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012;11(11):1006-12.

65. Bennett DA, Arnold SE, Valenzuela MJ, Brayne C, Schneider JA. Cognitive and social lifestyle: Links with neuropathology and cognition in late life. Acta Neuropathol. 2014;127(1):137-50.

66. Srinivasan S, Glover J, Tampi RR, Tampi DJ, Sewell DD. Sexuality and the Older Adult. Curr Psychiatry Rep. 2019;21(10):97.

67. Guo H, Siu W, D'Arcy RC, Black SE, Grajauskas LA, Singh S, et al. MRI assessment of whole-brain structural changes in aging. Clin Interv Aging. 2017;12:1251-70.

68. Dadar M, Maranzano J, Misquitta K, Anor CJ, Fonov VS, Tartaglia MC, et al. Performance comparison of 10 different classification techniques in segmenting white matter hyperintensities in aging. Neuroimage. 2017;157:233-49.

69. Babulal GM, Quiroz YT, Albensi BC, Arenaza-Urquijo E, Astell AJ, Babiloni C, et al. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: update and areas of immediate need. Alzheimers Dement. 2019;15(2):292-312.

70. Lehman BJ, David DM, Gruber JA. Rethinking the biopsychosocial model of health: understanding health as a dynamic system. Soc personal psychol compass. 2017;11(8):e12328.

Figure caption

Figure 1. Areas of voxel by voxel gray matter differences in opposite sex (top row) and same sex (bottom row) patients when compared with their healthy control counterpart

APPENDIX A - Availability of neuropsychological and clinical measures.

	Opposite-sex		Same-sex	
Characteristic	**HC (n=20)**	**PT (n=20)**	**HC (n=20)**	**PT (n=20)**
CDR	20	20	20	20
NPI-Q	20	20	20	18
GDS	19	19	20	20
MMSE/MoCA	11/9	13/7	9/11	12/8
SF	20	19	20	20
TMT-A	20	19	20	20
TMT-B	20	17	20	18
TMT-B-A	20	17	20	18
LMT-IR	19	19	20	19
LMT-DR	19	18	20	19
DST-F	20	20	20	20
DST-B	20	20	19	20

CDR: Clinical Dementia Rating; DS-F/B: Digit Span Test – forward and backward; GDS: Geriatric Depression Scale; HC: Healthy controls; LMT-IR/DR: Logical Memory Test – immediate and delayed recall; MMSE/MoCA: Mini Mental State Examination/Montreal Cognitive Assessment; NPI-Q: Neuropsychiatric Inventory Questionnaire; PT: Patients; SF: Semantic Fluency; TMT-A/B/B-A: Trail Making Test - part A, part B and difference B-A

APPENDIX B - MRI parameters of the T1-weighted scans included in the analysis

MR field strength (T)	Scanner manufacturer	Scanner model	Sequence	Acquisition	TR (ms)	TE (ms)	TI (ms)	Matrix size	Voxel size (mm)	Flip angle	Slices no.	Subjects no.
1.5	GE	SIGNA	FSPGE	N.A.	9	2	None	256 x 256	0.98 x 0.98 x 1.5	15	124	6
1.5	GE	SIGNA	N.A.	Coronal	35	2	None	256 x 256	0.78 x 0.78 x 1.6	60	124	4
1.5	GE	SIGNA HDx	FSPGE	N.A.	9	4	500	256 x 256	0.94 x 0.94 x 1.2	10	166	1
1.5	GE	SIGNA HDxt	FSPGE	Sagittal	10	4	500	256 x 256	0.94 x 0.94 x 1.2	10	156	3
1.5	GE	SIGNA HDxt	FSPGE	Sagittal	10	4	600	256 x 256	0.94 x 0.94 x 1.2	8	166	1
1.5	Phillips	Eclipse 1.5T	N.A.	N.A.	9	2	None	256 x 256	1 x 1 x 1.5	15	156	1
1.5	Phillips	Intera	N.A.	Sagittal	10	4	None	256 x 256	0.94 x 0.94 x 1.2	8	170	1
1.5	Siemens	Sonata	MPRAGE	N.A.	3	4	1000	192 x 192	1.25 x 1.25 x 1	8	160	1
1.5	Siemens	Sonata	MPRAGE	N.A.	1900	5	930	192 x 256	0.98 x 0.98 x 1	15	160	1
3	GE	DISCOVERY MR 750	FGE	Sagittal	7	3	450	256 x 256	1 x 1 x 1	12	176	2
3	GE	DISCOVERY MR 750	FSPGE	Sagittal	7	3	450	256 x 256	1 x 1 x 1	12	192	3
3	GE	DISCOVERY MR 750	FSPGE	Axial	8	3	450	256 x 256	1 x 1 x 1	12	156	22
3	GE	DISCOVERY MR 750	FSPGE	Sagittal	8	3	450	256 x 256	1 x 1 x 1	12	170	8
3	GE	DISCOVERY MR 750	FSPGE	Sagittal	8	3	900	256 x 256	0.98 x 0.98 x 1	9	176	2
3	GE	SIGNA EXCITE	N.A.	Sagittal	7	3	900	256 x 256	1.02 x 1.02 x 1.2	8	166	1
3	GE	SIGNA HDxt	N.A.	Sagittal	7	3	900	256 x 256	1.02 x 1.02 x 1.2	8	166	2
3	Phillips	Achieva	TFE	Sagittal	7	3	None	256 x 256	0.98 x 0.98 x 1.2	9	150	4
3	Siemens	Skyra	MPRAGE	Coronal	1380	3	700	256 x 256	0.98 x 0.98 x 1	9	176	2
3	Siemens	Skyra	MPRAGE	Coronal	1400	3	708	256 x 256	0.98 x 0.98 x 1	9	192	1
3	Siemens	Skyra	MPRAGE	Sagittal	2300	3	900	256 x 256	1 x 1 x 1.2	9	176	1
3	Siemens	Trio	MPRAGE	Axial	1620	4	950	192 x 256	0.98 x 0.98 x 1	15	160	1
3	Siemens	Trio Tim	MPRAGE	Sagittal	1310	2	900	256 x 256	0.98 x 0.98 x 1	10	144	1

3	Siemens	Trio Tim	MPRAGE	Sagittal	2300	3	900	240 x 256	1 x 1 x 1.2	9	160	2
3	Siemens	Trio Tim	MPRAGE	Sagittal	2500	3	1100	256 x 256	1 x 1 x 1	7	192	3
3	Siemens	Prisma	MPRAGE GRAPPA	Sagittal	2300	3	900	240 x 256	1.05 x 1.05 x 1.2	9	176	6

T: Tesla; FGE: Fast Gradient Echo; FSPGE: Fast Spoiled Gradient Echo; GRAPPA: Generalized Autocalibrating Partially Parallel Acquisition; MPRAGE: Magnetization Prepared Rapid Gradient Echo; N.A.: Not available; TE: Echo time; TFE: Turbo Field Echo; TI: Inversion time; TR: Repetition time

APPENDIX C - Differences in clinical and cognitive characteristics between patients and healthy controls within each relationship group ($p < 0.05$)

	Opposite-sex				Same-sex			
Characteristic	**HC (n = 20)**	**PT (n = 20)**	***F***	***p***	**HC (n = 20)**	**PT (n = 20)**	***F***	***p***
NPI-Q[a]	0.00 (1.00)	4.00 (7.00)	6.88	0.013	0.0 (0.00)	1.00 (3.00)	12.35	0.001
MMSE/MoCA	29.40 (0.68)	24.60 (4.20)	16.22	<0.001	29.40 (1.05)	24.80 (4.22)	10.01	0.003
SF	39.20 (7.17)	21.37 (8.98)	14.05	0.001	41.05 (6.77)	22.65 (9.26)	22.13	<0.001
TMT-A	24.35 (8.47)	39.53 (14.32)	4.46	0.057	23.70 (7.54)	54.00 (32.97)	3.10	0.088
TMT-B	52.25 (11.03)	130.24 (65.27)	9.66	0.004	53.90 (17.96)	156.94 (86.01)	7.24	0.016
TMT-B-A	27.90 (10.51)	92.47 (60.39)	8.25	0.007	30.20 (14.99)	107.83 (73.75)	5.71	0.023
LMT-IR	17.00 (3.77)	7.32 (4.28)	23.93	<0.001	16.05 (3.73)	8.95 (5.21)	13.31	0.001
LMT-DR	15.74 (4.70)	3.22 (3.67)	40.12	<0.001	14.85 (4.16)	5.05 (5.99)	14.53	0.001
DST-F[a]	7.00 (2.00)	6.00 (3.00)	0.83	0.370	7.00 (2.00)	6.00 (1.00)	0.54	0.467
DST-B[a]	6.00 (2.00)	5.00 (2.00)	0.24	0.628	5.00 (1.00)	4.00 (2.00)	5.36	0.027

Values are mean (standard deviation)

[a] Median (Interquartile range) for variables not normally distributed

DS-F/B: Digit Span Test – forward and backward; HC: Healthy controls; LMT-IR/DR: Logical Memory Test – immediate and delayed recall; MMSE/MoCA: Mini Mental State Examination/Montreal Cognitive Assessment; NPI-Q: Neuropsychiatric Inventory Questionnaire; PT: Patients; SF: Semantic Fluency; TMT-A/B/B-A: Trail Making Test - part A, part B and difference B-A

APPENDIX D - Differences in rates of psychiatric medications between patients and healthy controls within each relationship group ($p < 0.05$)

	Healthy controls				Patients			
Psychiatric medication	**OS (n =20)**	**SS (n =20)**	***χ2***	***p***	**OS (n =20)**	**SS (n =20)**	***χ2***	***p***
Any[a]	5/15	8/12	1.03	0.31	4/16	9/11	2.85	0.09
SNRI[a]	1/19	0/20	1.00	0.32	0/20	2/18	2.05	0.15
SSRI[a]	4/16	7/13	1.13	0.29	2/18	7/13	3.49	0.06
Beta Blockers[a]	1/19	0/20	1.00	0.32	0/20	0/20	0.00	1.00
TCA[a]	0/20	0/20	0.00	1.00	1/19	0/20	1.00	0.32
BDZ[a]	0/20	1/19	1.00	0.32	1/19	1/19	0.00	1.00
AA[a]	0/20	0/20	0.00	1.00	0/20	1/19	1.00	0.32

AA: Atypical antipsychotics; BDZ: Benzodiazepines; SNRI: Serotonin-norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants.

[a] Medicated cases: Yes/No

Abstract

Background: Individuals from sexual minorities experience health inequalities that have detrimental impacts on their health, especially in the elderly, by exacerbating care needs and symptoms of chronic conditions such as Alzheimer's disease (AD). Neurocognitive decline due to AD in the sexual minority population remains under-investigated. However, being in a relationship may mitigate the risk of experiencing cognitive impairment.

Objective: The aim of this study was to investigate whether cognitive decline and brain atrophy may differ in people from sexual minorities.

Methods: Clinical data for this study were selected from the National Alzheimer's Coordinating Center's Uniform Data Set and structural MRI data collected across 14 Alzheimer's Disease Centers. Eighty participants were included: 20 patients with AD and 20 healthy controls (HC) in same-sex relationships were identified and matched to groups of participants (20 AD and 20 HC) in opposite-sex relationships. The effects of diagnosis and relationship were investigated on all measures.

Results: No diagnosis-by-relationship interactions were found on any variable. However, *post hoc* analyses revealed that the opposite-sex group had grey matter atrophy mainly in medio-temporal areas, while in the same-sex group atrophy also extended to pre-frontal and cingulate areas. Severity of neuropsychiatric symptoms correlated with volume of pre-frontal and insular/temporal areas only in the same-sex group.

Conclusion: Neurocognitive decline due to AD may express similarly across individuals, independently of relationship type, thus suggesting a protective role of relational status. However, the same-sex group appeared to be more likely to experience at least one neuropsychiatric symptom and to have atrophy extending to fronto-limbic areas.

Keywords: Alzheimer's disease; neurodegeneration; marital relationship; sexual minorities; neuropsychiatric symptoms; cognition

1. Introduction

People belonging to sexual and gender minorities, i.e. people identifying as lesbian, gay, bisexual, transgender and other minorities (LGBT+), are more likely to face health inequalities than heterosexual people. This has been especially observed in the context of chronic diseases leading to greater detrimental effects as well as higher mortality rates (1). For example, cardiovascular risk factors are significantly more frequent in LGBT+ than in heterosexual people, especially among lesbian women (2), and this increased risk appears to be related mainly to exposure to early life adverse experiences (3). However, only very recently the first attempts have been made to set road-maps to investigate how health inequalities may exert long-lasting effects, particularly relevant for LGBT+ older adults (4). Despite the extensive literature on the LGBT+ youth, less attention has been dedicated to the ageing population. Indeed, the risk and the impact of dementia among sexual minorities are still largely overlooked issues (5, 6).

The last Alzheimer's Association Report mentioned social isolation as the main challenge for older LGBT+ people (7), who in general appear to have higher risk of life-time depression despite reporting better self-rated health (8). Qualitative investigations into the needs and the socio-legal issues faced by older adults from sexual minorities living with dementia showed that the relationship with their families and care-givers is crucial to determine patients' willingness to disclose their sexual orientation in healthcare settings and, hence, have access to appropriate care plans (9-11).

Neurocognitive functioning in the LGBT+ ageing population has rarely been investigated, probably due to the widespread lack of systematic collection of data on sexual orientation and gender identity in healthcare services (4). Recently, a cross-sectional population-based investigation carried out in the United States observed that people from sexual and gender minorities above 45 years of age were not more likely to report subjective cognitive decline compared to heterosexual people (12). However, non-white ethno-racial background and history of depression have been significantly associated with higher likelihood for LGBT+ older adults to present with subjective cognitive complaints (13). Moreover, a study found that the risk of mild cognitive impairment (MCI) and dementia appears to be similar between people in same-sex and opposite-sex relationships, thus suggesting that being in a relationship may be a protective factor against cognitive decline in individuals from sexual and gender minorities (14).

Currently, to the best of our knowledge, no findings have been published yet on whether neurodegeneration and cognitive and functional decline express similarly between heterosexual and non-heterosexual older adults.

Therefore, the present study aimed at comparing cognitive functioning, neuropsychiatric symptoms and patterns of neurodegeneration between people in same-sex and opposite-sex relationships.

2. Methods

2.1. Database description

The sample of individuals included in this study was selected by consulting the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), i.e. a standardized database of clinical data collected by a number of NIA-funded Alzheimer's Disease Centers (ADCs) in the United States (15, 16). Each center received approval for data collection by its own institutional review board prior to submitting data to NACC. All ADCs obtained informed consent from participants recruited. Participants were also asked to identify a study partner they were in contact with regularly to answer questions about the participants' health status. No additional ethical approval was required locally since the NACC database includes data that are anonymized and publicly available for download upon request.

2.2. Sample selection

Participants with UDS data collected between September 2005 and August 2019 were screened. A selection procedure analogous to another study (14) was followed to identify individuals from sexual minorities by comparing the sex reported by each participant and his/her spouse/partner, if presenting as the study partner. Where more than one visit was available, individuals were considered either in a same-sex or opposite-sex relationship if they reported such status consistently throughout the different assessment visits. Therefore, sexual orientation (heterosexual vs non-heterosexual) of participants included in this study was implied by their relationship status (opposite-sex vs same-sex).

The following inclusion criteria were used: 1) availability of a T1-weighted magnetic resonance imaging (MRI) scan taken +/-3 months from a UDS visit; 2) either normal cognition at all UDS visits or a primary clinical diagnosis of mild cognitive impairment/dementia due to AD at the UDS visit closest to the MRI scan; 3) availability of a study partner identified as a spouse/partner of the same sex of the study participant at any assessment visits. As a results, forty-one participants in same-sex relationships were identified: 21 healthy people and 20 patients with MCI/dementia due to AD. After quality-check of structural MRI data, one healthy participant had to be discarded because of the low quality of available data. Additionally, two groups of individuals (20 healthy and 20 MCI/AD) in an opposite-sex relationship were selected to be matched to those in

a same-sex relationship by sex, age, years of education, global cognitive functioning status, diagnosis, and APOE status.

2.3. Neuropsychological and clinical assessment

UDS data are collected by trained clinicians and clinic personnel from participants and their study partners about demographics, medical history, clinical examinations, functional and behavioral assessments, dementia severity, and a comprehensive neuropsychological evaluation. The diagnostic process varies across ADCs and a final clinical diagnosis is reached by either a team or a single physician who conducted the examination. Criteria initially used to diagnose MCI (17) and dementia due to AD (18) were updated in Version 3 of the UDS (19-21). Severity of dementia was measured by means of the CDR® Dementia Staging Instrument global score (22). The neuropsychological assessment protocol evolved and was updated in Version 3 of the UDS by replacing some of the cognitive tests (23, 24). For this reason, a selection of tests available for most participants included was made as follows (see Appendix A for details on test availability): Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) (MoCA scores were converted into MMSE scores following published norms (25) to allow comparison across all participants); Semantic Fluency Test (average of total correct items in two categories: animals and vegetables), Trail Making Test (part A, part B and difference B-A), Logical Memory Test (immediate and delayed recall), Digit Span Test (forward and backward recall). Additionally, the presence of neuropsychiatric symptoms was recorded by means of the Neuropsychiatric Inventory Questionnaire (NPI-Q) (26) and the Geriatric Depression Scale (GDS) (27).

2.4. APOE genetic profile

Biomarker data at NACC are best described as a convenience sample that is voluntarily submitted by individual ADCs. In general, no submission deadlines for data collection periods are defined for biomarker data. APOE genotype investigation is carried out independently by each ADC and by the Alzheimer's Disease Genetics Consortium (ADGC) and the National Institute of Aging Genetics of Alzheimer's Disease Data Storage Site (NCRAD) and later reported to NACC. If there is disagreement between the genetic profiling results submitted by the ADC and those submitted by the ADGC, the APOE genotype is considered as missing.

2.5. MRI parameters and pre-processing

MRI data collected as part of the NACC imaging database are also best defined as a convenience sample of images that are voluntarily submitted by each single ADC to NACC. Collection and acquisition protocols are variable across ADCs and may include different MRI scans. The focus of this study was on gray matter (GM) neurodegeneration and, thus, only structural T1-weighted MRI data collected in 14 ADCs were included in our analyses. Specifications about acquisition parameters and scanner characteristics are reported in Appendix B.

In consideration of the limited sample size of the groups selected according to our inclusion criteria, a decision was made to pool together scans acquired at different magnetic field strengths (19 at 1.5T and 61 at 3T). This represents a common practice as part of the increasing number of initiatives aimed at sharing neuroimaging data acquired on different MRI scanners across multiple sites across the world, such as the NACC and the Alzheimer's Disease Neuroimaging Initiative (ADNI) databases. Indeed, it has been shown that acquisition of structural MRI brain images of healthy people and patients with AD acquired on the same platform, but with different scanners and using different acquisition parameters, has significantly smaller effects than those of the disease itself (28). Moreover, although the combined analysis of structural images acquired at different MR field strengths may have a significant effect on the volumetric assessment of the cerebellum, the precentral gyrus and the thalamus bilaterally, no interaction was observed with disease status, i.e. findings about AD-related atrophy appear to be replicable and reliably detectable independently of the MR field strength in analysis of pooled structural MRI data (29). Consistently, Schmitter et al. (30) found very similar results regarding the classification of patients with MCI and dementia due to AD using two alternative datasets of T1-weighted images: either all acquired at 1.5T or when mixing images acquired at 1.5T and 3T.

All T1-weighted images were pre-processed using a standard voxel-based morphometry procedure (31). First, scans were segmented in order to obtain three tissue maps: GM, white matter (WM) and cerebrospinal fluid (CSF). Second, GM tissue maps were corrected for magnetic field inhomogeneities (32). Third, bias-corrected images were normalized to the standard ICBM template in the MNI space. Fourth, normalized GM maps were smoothed by applying an isotropic Gaussian kernel of 8 mm. All voxel-based morphometry pre-processing and analysis steps were carried out in SPM12 (Wellcome Centre for Human Neuroimaging, London, UK - https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running on Matlab R2016b (The Mathworks, Natick, Massachusetts, USA). The volume of the segmented tissue maps in milliliters was extracted for all participants using the SPM function *get_totals*. In order to account for variability in the MRI acquisition parameters, for

each participant a GM fraction was calculated as the proportion of GM volume divided by the total intracranial volume (sum of the GM, WM and CSF volumes).

2.6. Statistical analysis

All statistical analyses on clinical variables were carried out in SPSS version 26 (IBM, Chicago, IL, USA). Interactions between diagnosis (healthy vs MCI/AD) and relationship (same-sex vs opposite-sex) on both clinical ($p < 0.05$) and structural MRI ($p < 0.05$ FWE) measures were investigated using a 2x2 ANCOVA with age as a covariate, since it was the only variable differing between patients and healthy participants. Sex was also included in the model due to the unbalanced sex distributions in the study sample that could potentially bias the results. Finally, MRI field strength was also added as a covariate in MRI analysis since scanners of different field strength have been used across ADCs. Sub-group analyses were carried out limitedly to those participants with known APOE genotype in order to prevent biased findings due to a possible unbalanced distribution of APOE genotypes.

Additional *post hoc* analyses were carried out to ascertain potential differences in clinical profile, cognitive performance, and GM volume between patients and healthy participants in the same-sex and opposite-sex groups separately. Moreover, the volume of the GM clusters significantly smaller in patients compared to healthy participants in a same-sex relationship was extracted, divided by the total intracranial volume, and partial correlations between these volume ratios and NPI scores, using age as covariate, were investigated.

3. Results

3.1. Clinical and cognitive results

A total of 80 participants, 40 healthy controls and 40 patients with MCI/AD, were included in this study. Participants in same-sex and opposite-sex relationships, both patients and controls, were matched for all clinical and cognitive characteristics (Table 1). Compared to healthy controls, patients were older (years of age: 57.93 ± 11.14 vs 72.47 ± 10.18), had less GM overall, presented with worse cognitive performance on all tests and had higher NPI-Q scores (Table 2). Marginal differences were also noted in sex (20 males and 20 females among patients, but 29 males and 11 females among controls) and APOE genotype distributions that, however, depended on subjects' availability in the NACC database. No differences in racial composition were found between either patients or relationship groups, with the vast majority of participants reporting a white racial background.

- Insert Table **1** about here -

No diagnosis-by-relationship interaction effect was detected for scores on either the neuropsychological tests, the NPI-Q or the GDS. Indeed, patients in opposite-sex and same-sex relationships showed similar profiles of cognitive decline when investigated separately across all tests apart from the Digit Span Test, and patients in same-sex relationships also showed significantly lower scores on the Digit Span Test – backward ($F = 5.36$, $p = 0.03$) (Appendix C). In fact, no differences were observed in either CDR or cognitive test scores between patients in different relationships (Table 1). Moreover, although both groups of patients were significantly more likely than healthy controls to present with at least one neuropsychiatric symptom, this was highly significant in the same-sex group ($\chi^2 = 13.48$, $p < 0.001$), but only marginally in the opposite-sex group ($\chi^2 = 5.01$, $p = 0.02$). Instead, no differences in the rates of use of psychiatric medications were found between different relational groups (Appendix D). All of these results were replicated also when analyses were restricted only to participants with known APOE status.

- Insert Table **2** about here -

3.2. VBM results

The samples of participants in same-sex and opposite-sex relationships were matched for the proportion of brain images acquired at either 1.5T or 3T ($\chi2 = 0.069$, $p = 0.793$): nine 1.5T and thirty-one 3T images for the opposite-sex group, ten 1.5T and thirty 3T images for the same-sex group. Within the two relational groups, MRI field strengths were also equally distributed between the two diagnostic groups: $\chi2 = 3.58$, $p = 0.058$ for the OS group and $\chi2 = 2.13$, $p = 0.144$ for the SS group.

VBM analysis of T1-weighted scans revealed no relationship-by-diagnosis interaction effect as well as lack of a main effect of relationship type on regional GM volumes. Instead, diffuse GM loss was observed in the overall comparison between patients with MCI/dementia due to AD and healthy controls bilaterally in the temporal lobe, insula, posterior cingulate, occipito-temporal and medial prefrontal cortices (Table 3). However, the analyses carried out on participants in different relationship groups separately revealed different patterns of atrophy: patients in opposite-sex relationships showed mainly atrophy in the medial temporal lobe (MTL) bilaterally and the right insula/ superior temporal gyrus (STG); while the same-sex group had atrophy in the left

medial temporal lobe, the left insula/STG, medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) bilaterally (Figure 1; Table 2). The results survived also when participants with unknown APOE genotype were excluded from the analysis.

Volume ratios were calculated for four clusters of significantly greater GM atrophy in patients compared to healthy controls in same-sex relationships: the left MTL, the left insula/STG, the PCC and the mPFC bilaterally (Table 2). Overall, NPI scores were negatively correlated with volumes of two seeds: the left insula/STG ($\rho = -0.32$, $p < 0.01$) and the mPFC ($\rho = -0.34$, $p < 0.01$). NPI scores were not correlated with volume ratios of any seeds when participants were divided by diagnosis. However, when analyses were carried out on the overall sample, divided by relationship type, the pattern of associations was different: in the opposite-sex group, no significant negative correlations were detected for any of the seeds; while in the same-sex group NPI scores were correlated negatively with both the left insula/STG ($\rho = -0.41$, $p = 0.01$) and the mPFC volume ratios ($\rho = -0.42$, $p = 0.01$). No significant associations between regional GM volumes and GDS scores were observed.

- Insert **Figure 1** and **Table 2** about here -

4. Discussion

In this study we found that diagnosis of cognitive impairment due to AD does not interact with type of relationship in determining profiles of cognitive decline, neuropsychiatric symptoms, and neurodegeneration. However, when people in either opposite-sex or same-sex relationships were analyzed separately, different patterns of GM atrophy were detected in the comparison between patients and healthy controls. In fact, participants in a same-sex relationship had more pronounced GM atrophy in pre-frontal and posterior cingulate areas that was not observed for patients in the opposite-sex group. All significant findings survived after restricting the analyses only to those participants with known APOE genotype.

The same-sex group of patients was also far more likely to experience at least one neuropsychiatric symptom than healthy controls, while for the opposite-sex group this finding was only weakly significant. The higher propensity of the same-sex group to experience neuropsychiatric symptoms, although the total NPI and GDS scores were similar to those of the opposite-sex group, may account for the different patterns of atrophy. Indeed, the NPI score correlated with the volume of the left insula/STG and bilateral mPFC clusters only in the same-sex group, but not in the opposite-sex group. Interestingly, an association between atrophy in these areas and the presence of multiple neuropsychiatric symptoms in patients with AD has been previously observed, especially in

frontal areas (33-35). Consistently, functional connectivity alterations in fronto-parietal areas (36, 37) and metabolic dysfunction in limbic areas have also been linked to the emergence of neuropsychiatric symptoms across different stages of AD (38, 39).

Providing an explanation to account for a trend towards higher prevalence of neuropsychiatric symptoms in the same-sex group of patients is out of the scope of our investigations. Nonetheless, it must be noted that factors other than AD-related core neuropathological processes may independently contribute to the emergence of neuropsychiatric symptoms in this clinical population, such as genetic and environmental factors (35, 40). In the present study, we matched participants for APOE genotype since the ε4 allele has been suggested to represent a risk factor not only for AD itself, but also for neuropsychiatric symptoms, although current evidence is still inconsistent (41, 42). Moreover, no differences in rates of psychiatric medications, that might affect regional GM volumes, were found between relational groups. Therefore, we may suggest that environmental factors, probably related to personal history, might have played a role in determining different sub-threshold trajectories of GM degeneration between the opposite-sex and same-sex groups of patients in relation to neuropsychiatric manifestations. These findings emerged only when comparing patients with controls within relational groups either because of the small sample size or because these differences are very subtle and, therefore, are overshadowed by the main AD-related neuropathological changes when comparing the two patient groups directly.

Currently, the main theoretical framework used to explain ageing trajectories (43) and worse cognitive outcomes (44) in non-heterosexual compared to heterosexual older adults is minority stress. Minority stress is a theoretical construct to describe a stressful social environment experienced by people belonging to stigmatized minority groups, that in the case of sexual minorities it is thought to involve: experience of discrimination, expectation of discrimination based on sexual orientation, internalization of the stigma brought about by society, and concealment of sexual orientation (45). A flourishing literature has previously shown how minority stress in LGBT+ people has detrimental effects on both mental (46) and physical health (47), and can also lead to alterations in gene expression (48). For these reasons, minority stress is hypothesized to disrupt behavior and biological processes that, in turn, may impact cognitive functioning (49). Moreover, chronic stress and stress-related disorders have also been found to affect a variety of brain areas, particularly prefrontal and orbitofrontal cortices, as well as temporal and cingulate areas (50-52). Therefore, higher levels of stress experienced as a consequence of discrimination may be affecting individuals from sexual minorities and predispose them to higher rates of frontal and limbic atrophy and, in turn, higher rates of neuropsychiatric symptoms within the

context of a neurodegenerative condition. In fact, we found negative correlations between NPI scores and volumes of mPFC and left insula/STG, areas involved in emotional, behavioral and interoceptive processing. The lack of significant results in the direct comparison between relationship groups may be imputed mainly to the small sample size of the groups of participants: a factor that, however, depended on participants' availability in the NACC database. However, all participants included in our study were selected among those in a relationship with a partner/spouse. As mentioned above, LGBT+ older adults are at higher risk of social isolation and, therefore, our sample may represent a very specific sub-group within the wider LGBT+ elderly population. Interestingly, marital status seems to decrease the risk of dementia for people in a relationship (53, 54), and even to contribute to better treatment response (55). A possible explanation is that being in a long-term relationship represents a protective factor against minority stress and consequently reduces loneliness, i.e. perceived social isolation, and its negative consequences in LGBT+ elderly (56). Indeed, a variety of studies have reported that loneliness and social isolation may be independently associated with worse cognitive decline, particularly in memory functions (57-59), and with increased risk of AD (60, 61). These findings have also been corroborated by animal models of AD that have shown worse neural and behavioral outcomes as a consequence of social isolation (62). Recently, the first study to investigate the impact of social isolation on the brain of older adults found that experience of social isolation correlated negatively with GM volume in areas of the left MTL that are crucially involved in emotion processing and memory functions and particularly affected by AD pathology (63). It appears plausible, therefore, that being in a long-term relationship, either opposite-sex or same-sex, may mitigate the negative impact of either environmental (e.g. minority stress and social isolation) or biological (e.g. AD pathology) factors on cognitive functioning in line with the findings by Perales-Puchalt et al. (14). This may occur because long-term relationships offer the conditions to sustain optimal levels of social engagement, which is considered a fundamental aspect contributing to cognitive reserve (64) by attenuating the impact of neurodegeneration on cognitive performance (65).

A first limitation of this study is the identification of participants belonging to sexual minorities based on their relationship status, similarly to the procedure followed by Perales-Puchalt et al. (14). Although this approach has been previously used, we cannot exclude a potential selection bias. Indeed, due to the lack of data on sexual orientation as part of the NACC USD, non-heterosexual orientation (either homosexual or bisexual) was assumed for people in same-sex relationships, but we could not rule out that some participants in the opposite-sex group might have concealed their sexual orientation, a main issue in research on LGBT+ older adults (66). Second, individuals who were not in a relationship or did not have their partner/spouse as study partner were

excluded because it was not possible to infer their sexual orientation. This had two consequences: generation of groups with a small sample size and lack of a control group of non-heterosexual individuals not in a relationship, thus limiting the generalizability of our findings to the whole LGBT+ elderly population affected by AD and the interpretation of the potentially protective role of marital status. Third, the high variability in MRI acquisition protocols across ADCs warrants caution in interpreting and generalizing our VBM findings. However, it must be highlighted that the results we found were consistent with the pattern of atrophy expected from a comparison between patient with AD and healthy controls. Indeed, structural MRI data from the NACC database have already been used in multi-database studies to quantify whole-brain changes in ageing (67) and WM hyper-intensities (68), yielding results consistent across publicly available databases. Additionally, MRI magnetic field strength was added as a covariate in the VBM analyses as one of the main parameters that may affect image resolution. Moreover, we corrected all GM volumes extracted by dividing them by the total intracranial volume, thus minimizing any potential global volumetric differences due to discrepancies in MRI acquisition parameters.

5. Conclusion

Our preliminary findings suggest that people with AD from sexual minorities may experience more neuropsychiatric symptoms associated to GM atrophy mainly in pre-frontal areas, additional to AD-related MTL degeneration. Further prospective investigations in larger samples are needed to ascertain this trend and the inclusion of people without a partner/spouse would be beneficial to test whether being in a relationship may represent a protective factor against AD pathology and symptoms associated with it for LGBT+ elderly. Considering the complete lack of data, targeted investigations are also needed to investigate aging and dementia in transgender people. Findings already established on ethno-racial minorities with dementia (69) may provide a fruitful foundation of knowledge to translate into a new research line about the investigation of sexual (and gender) minority stress as a risk factor for cognitive decline within the wider framework of the dynamic bio-psycho-social model (70).

Conflict of interest

The authors report no conflict of interest.

References

1. Bristowe K, Hodson M, Wee B, Almack K, Johnson K, Daveson BA, et al. Recommendations to reduce inequalities for LGBT people facing advanced illness: ACCESSCare national qualitative interview study. Palliat Med. 2018;32(1):23-35.

2. Caceres BA, Brody A, Luscombe RE, Primiano JE, Marusca P, Sitts EM, et al. A systematic review of cardiovascular disease in sexual minorities. Am J Public Health. 2017;107(4):e13-21.

3. Hatzenbuehler ML, Slopen N, McLaughlin KA. Stressful life events, sexual orientation, and cardiometabolic risk among young adults in the United States. Health Psychol. 2014;33(10):1185-94.

4. Westwood S, Willis P, Fish J, Hafford-Letchfield T, Semlyen J, King A, et al. Older LGBT+ health inequalities in the UK: setting a research agenda. J Epidemiol Community Health. 2020.

5. McGovern J. The forgotten: dementia and the aging LGBT community. J Gerontol Soc Work. 2014;57(8):845-57.

6. Rosendale N, Josephson SA. The importance of lesbian, gay, bisexual, and transgender health in neurology: what's in a name? JAMA Neurol. 2015;72(8):855-6.

7. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. Alzheimers Dement. 2019;15(3):321-87.

8. Nelson CL, Andel R. Does sexual orientation relate to health and well-being? Analysis of adults 50+ years of age. Gerontologist. 2020.

9. Barrett C, Crameri P, Lambourne S, Latham JR, Whyte C. Understanding the experiences and needs of lesbian, gay, bisexual and trans Australians living with dementia, and their partners. Australas J Ageing. 2015;34 Suppl 2:34-8.

10. Fredriksen-Goldsen KI, Jen S, Bryan AEB, Goldsen J. Cognitive impairment, Alzheimer's disease, and other dementias in the lives of lesbian, gay, bisexual and transgender (LGBT) older adults and their caregivers: needs and competencies. J Appl Gerontol. 2018;37(5):545-69.

11. Peel E, Taylor H, Harding R. Sociolegal and practice implications of caring for LGBT people with dementia. Nurs Older People. 2016;28(10):26-30.

12. Brown MJ, Patterson R. Subjective cognitive decline among sexual and gender minorities: results from a U.S. population-based sample. J Alzheimers Dis. 2020;73(2):477-87.

13. Flatt JD, Johnson JK, Karpiak SE, Seidel L, Larson B, Brennan-Ing M. Correlates of subjective cognitive decline in lesbian, gay, bisexual, and transgender older adults. J Alzheimers Dis. 2018;64(1):91-102.

14. Perales-Puchalt J, Gauthreaux K, Flatt J, Teylan MA, Resendez J, Kukull WA, et al. Risk of dementia and mild cognitive impairment among older adults in same-sex relationships. Int J Geriatr Psychiatry. 2019;34(6):828-35.

15. Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. Alzheimer Dis Assoc Disord. 2007;21(3):249-58.

16. Besser L, Kukull W, Knopman DS, Chui H, Galasko D, Weintraub S, et al. Version 3 of the National Alzheimer's Coordinating Center's Uniform Data Set. Alzheimer Dis Assoc Disord. 2018;32(4):351-8.

17. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56(3):303-8.

18. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-44.

19. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270-9.

20. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-9.

21. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92.

22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412-4.

23. Morris JC, Weintraub S, Chui HC, Cummings J, Decarli C, Ferris S, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006;20(4):210-6.

24. Weintraub S, Besser L, Dodge HH, Teylan M, Ferris S, Goldstein FC, et al. Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). Alzheimer Dis Assoc Disord. 2018;32(1):10-7.

25. Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE. Comparative accuracies of two common screening instruments for the classification of Alzheimer's disease, mild cognitive impairment and healthy aging. Alzheimers Dement. 2013;9(5):529-37.

26. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12(2):233-9.

27. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol J Aging Ment Heal. 1986;5(1-2):165-73.

28. Stonnington CM, Tan G, Klöppel S, Chu C, Draganski B, Jack CR, Jr., et al. Interpreting scan data acquired from multiple scanners: a study with Alzheimer's disease. Neuroimage. 2008;39(3):1180-5.

29. Marchewka A, Kherif F, Krueger G, Grabowska A, Frackowiak R, Draganski B. Influence of magnetic field strength and image registration strategy on voxel-based morphometry in a study of Alzheimer's disease. Hum Brain Mapp. 2014;35(5):1865-74.

30. Schmitter D, Roche A, Maréchal B, Ribes D, Abdulkadir A, Bach-Cuadra M, et al. An evaluation of volume-based morphometry for prediction of mild cognitive impairment and Alzheimer's disease. Neuroimage Clin. 2015;7:7-17.

31. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000;11(6 Pt 1):805-21.

32. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26(3):839-51.

33. Boublay N, Schott AM, Krolak-Salmon P. Neuroimaging correlates of neuropsychiatric symptoms in Alzheimer's disease: a review of 20 years of research. Eur J Neurol. 2016;23(10):1500-9.

34. Boublay N, Bouet R, Dorey JM, Padovan C, Makaroff Z, Federico D, et al. Brain volume predicts behavioral and psychological symptoms in Alzheimer's disease. J Alzheimers Dis. 2020;73(4):1343-53.

35. Poulin SP, Bergeron D, Dickerson BC. Risk factors, neuroanatomical correlates, and outcome of neuropsychiatric symptoms in Alzheimer's disease. J Alzheimers Dis. 2017;60(2):483-93.

36. Munro CE, Donovan NJ, Guercio BJ, Wigman SE, Schultz AP, Amariglio RE, et al. Neuropsychiatric symptoms and functional connectivity in mild cognitive impairment. J Alzheimers Dis. 2015;46(3):727-35.

37. Wang X, Ren P, Mapstone M, Conwell Y, Porsteinsson AP, Foxe JJ, et al. Identify a shared neural circuit linking multiple neuropsychiatric symptoms with Alzheimer's pathology. Brain Imaging Behav. 2019;13(1):53-64.

38. Ballarini B, Iaccarino L, Magnani G, Nagehan A, Miller BL, Jagust WJ, et al. Neuropsychiatric subsyndromes and brain metabolic network dysfunctions in early onset Alzheimer's disease. Hum Brain Mapp. 2016;37(12):4234-47.

39. Ng KP, Pascoal TA, Mathotaarachchi S, Chung CO, Benedet AL, Shin M, et al. Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease. Neurology. 2017;88(19):1814-21.

40. Showraki A, Murari G, Ismail Z, Barfett JJ, Fornazzari L, Munoz DG, et al. Cerebrospinal fluid correlates of neuropsychiatric symptoms in patients with Alzheimer's disease/mild cognitive impairment: a systematic review. J Alzheimers Dis. 2019;71(2):477-501.

41. Christie D, Shofer J, Millard SP, Li E, Demichele-Sweet MA, Weamer EA, et al. Genetic association between APOE*4 and neuropsychiatric symptoms in patients with probable Alzheimer's disease is dependent on the psychosis phenotype. Behav Brain Funct. 2012;8:62.

42. D'Onofrio G, Panza F, Seripa D, Sancarlo D, Paris F, Cascavilla L, et al. The APOE polymorphism in Alzheimer's disease patients with neuropsychiatric symptoms and syndromes. Int J Geriatr Psychiatry. 2011;26(10):1062-70.

43. Fabbre VD, Jen S, Fredriksen-Goldsen K. The state of theory in LGBTQ aging: implications for gerontological scholarship. Res Aging. 2019;41(5):495-518.

44. Correro IL AN, Nielson KA. A review of minority stress as a risk factor for cognitive decline in lesbian, gay, bisexual, and transgender (LGBT) elders. J Gay Lesbian Ment Health. 2019;24(1):2-19.

45. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull. 2003;129(5):674-97.

46. Bostwick WB, Boyd CJ, Hughes TL, West BT, McCabe SE. Discrimination and mental health among lesbian, gay, and bisexual adults in the United States. Am J Orthopsychiatry. 2014;84(1):35-45.

47. Lick DJ, Durso LE, Johnson KL. Minority stress and physical health among sexual minorities. Perspect Psychol Sci. 2013;8(5):521-48.

48. Flentje A, Kober KM, Carrico AW, Neilands TB, Flowers E, Heck NC, et al. Minority stress and leukocyte gene expression in sexual minority men living with treated HIV infection. Brain Behav Immun. 2018;70:335-45.

49. Forrester SN, Gallo JJ, Whitfield KE, Thorpe RJ. A framework of minority stress: from physiological manifestations to cognitive outcomes. Gerontologist. 2019;59(6):1017-23.

50. Gianaros PJ, Jennings JR, Sheu LK, Greer PJ, Kuller LH, Matthews KA. Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. Neuroimage. 2007;35(2):795-803.

51. Guo P, Wang S, Chen C, Tian H, Li J, Zheng W, et al. Aberrant brain grey matter volume patterns differ among Chinese Han drug-naïve depression patients with acute and chronic stress. Oncotarget. 2017;8(54):91958-64.

52. Holmes SE, Scheinost D, DellaGioia N, Davis MT, Matuskey D, Pietrzak RH, et al. Cerebellar and prefrontal cortical alterations in PTSD: structural and functional evidence. Chronic Stress. 2018;2:2470547018786390.

53. Helmer C, Damon D, Letenneur L, Fabrigoule C, Barberger-Gateau P, Lafont S, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology. 1999;53(9):1953-8.

54. Sundström A, Westerlund O, Mousavi-Nasab H, Adolfsson R, Nilsson LG. The relationship between marital and parental status and the risk of dementia. Int Psychogeriatr. 2014;26(5):749-57.

55. Gallucci M, Spagnolo P, Aricò M, Grossi E. Predictors of response to cholinesterase inhibitors treatment of Alzheimer's disease: date mining from the TREDEM registry. J Alzheimers Dis. 2016;50(4):969-79.

56. Kuyper L, Fokkema T. Loneliness among older lesbian, gay, and bisexual adults: the role of minority stress. Arch Sex Behav. 2010;39(5):1171-80.

57. Lara E, Caballero FF, Rico-Uribe LA, Olaya B, Haro JM, Ayuso-Mateos JL, et al. Are loneliness and social isolation associated with cognitive decline? Int J Geriatr Psychiatry. 2019;34(11):1613-22.

58. Shankar A, Hamer M, McMunn A, Steptoe A. Social isolation and loneliness: relationships with cognitive function during 4 years of follow-up in the English Longitudinal Study of Ageing. Psychosom Med. 2013;75(2):161-70.

59. Tilvis RS, Kähönen-Väre MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. J Gerontol A Biol Sci Med Sci. 2004;59(3):268-74.

60. Rafnsson SB, Orrell M, d'Orsi E, Hogervorst E, Steptoe A. Loneliness, social integration, and incident dementia over 6 years: prospective findings from the English Longitudinal Study of Ageing. J Gerontol B Psychol Sci Soc Sci. 2020;75(1):114-24.

61. Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry. 2007;64(2):234-40.

62. Hsiao YH, Chang CH, Gean PW. Impact of social relationships on Alzheimer's memory impairment: mechanistic studies. J Biomed Sci. 2018;25(1):3.

63. Düzel S, Drewelies J, Gerstorf D, Demuth I, Steinhagen-Thiessen E, Lindenberger U, et al. Structural brain correlates of loneliness among older adults. Sci Rep. 2019;9.

64. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012;11(11):1006-12.

65. Bennett DA, Arnold SE, Valenzuela MJ, Brayne C, Schneider JA. Cognitive and social lifestyle: Links with neuropathology and cognition in late life. Acta Neuropathol. 2014;127(1):137-50.

66. Srinivasan S, Glover J, Tampi RR, Tampi DJ, Sewell DD. Sexuality and the Older Adult. Curr Psychiatry Rep. 2019;21(10):97.

67. Guo H, Siu W, D'Arcy RC, Black SE, Grajauskas LA, Singh S, et al. MRI assessment of whole-brain structural changes in aging. Clin Interv Aging. 2017;12:1251-70.

68. Dadar M, Maranzano J, Misquitta K, Anor CJ, Fonov VS, Tartaglia MC, et al. Performance comparison of 10 different classification techniques in segmenting white matter hyperintensities in aging. Neuroimage. 2017;157:233-49.

69. Babulal GM, Quiroz YT, Albensi BC, Arenaza-Urquijo E, Astell AJ, Babiloni C, et al. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: update and areas of immediate need. Alzheimers Dement. 2019;15(2):292-312.

70. Lehman BJ, David DM, Gruber JA. Rethinking the biopsychosocial model of health: understanding health as a dynamic system. Soc personal psychol compass. 2017;11(8):e12328.

Figure caption

Figure 1. Areas of voxel by voxel gray matter differences in opposite sex (top row) and same sex (bottom row) patients when compared with their healthy control counterpart

APPENDIX A - Availability of neuropsychological and clinical measures.

	Opposite-sex		Same-sex	
Characteristic	**HC (n=20)**	**PT (n=20)**	**HC (n=20)**	**PT (n=20)**
CDR	20	20	20	20
NPI-Q	20	20	20	18
GDS	19	19	20	20
MMSE/MoCA	11/9	13/7	9/11	12/8
SF	20	19	20	20
TMT-A	20	19	20	20
TMT-B	20	17	20	18
TMT-B-A	20	17	20	18
LMT-IR	19	19	20	19
LMT-DR	19	18	20	19
DST-F	20	20	20	20
DST-B	20	20	19	20

CDR: Clinical Dementia Rating; DS-F/B: Digit Span Test – forward and backward; GDS: Geriatric Depression Scale; HC: Healthy controls; LMT-IR/DR: Logical Memory Test – immediate and delayed recall; MMSE/MoCA: Mini Mental State Examination/Montreal Cognitive Assessment; NPI-Q: Neuropsychiatric Inventory Questionnaire; PT: Patients; SF: Semantic Fluency; TMT-A/B/B-A: Trail Making Test - part A, part B and difference B-A

APPENDIX B - MRI parameters of the T1-weighted scans included in the analysis

MR field strength (T)	Scanner manufacturer	Scanner model	Sequence	Acquisition	TR (ms)	TE (ms)	TI (ms)	Matrix size	Voxel size (mm)	Flip angle	Slices no.	Subjects no.
1.5	GE	SIGNA	FSPGE	N.A.	9	2	None	256 x 256	0.98 x 0.98 x 1.5	15	124	6
1.5	GE	SIGNA	N.A.	Coronal	35	2	None	256 x 256	0.78 x 0.78 x 1.6	60	124	4
1.5	GE	SIGNA HDx	FSPGE	N.A.	9	4	500	256 x 256	0.94 x 0.94 x 1.2	10	166	1
1.5	GE	SIGNA HDxt	FSPGE	Sagittal	10	4	500	256 x 256	0.94 x 0.94 x 1.2	10	156	3
1.5	GE	SIGNA HDxt	FSPGE	Sagittal	10	4	600	256 x 256	0.94 x 0.94 x 1.2	8	166	1
1.5	Phillips	Eclipse 1.5T	N.A.	N.A.	9	2	None	256 x 256	1 x 1 x 1.5	15	156	1
1.5	Phillips	Intera	N.A.	Sagittal	10	4	None	256 x 256	0.94 x 0.94 x 1.2	8	170	1
1.5	Siemens	Sonata	MPRAGE	N.A.	3	4	1000	192 x 192	1.25 x 1.25 x 1	8	160	1
1.5	Siemens	Sonata	MPRAGE	N.A.	1900	5	930	192 x 256	0.98 x 0.98 x 1	15	160	1
3	GE	DISCOVERY MR 750	FGE	Sagittal	7	3	450	256 x 256	1 x 1 x 1	12	176	2
3	GE	DISCOVERY MR 750	FSPGE	Sagittal	7	3	450	256 x 256	1 x 1 x 1	12	192	3
3	GE	DISCOVERY MR 750	FSPGE	Axial	8	3	450	256 x 256	1 x 1 x 1	12	156	22
3	GE	DISCOVERY MR 750	FSPGE	Sagittal	8	3	450	256 x 256	1 x 1 x 1	12	170	8
3	GE	DISCOVERY MR 750	FSPGE	Sagittal	8	3	900	256 x 256	0.98 x 0.98 x 1	9	176	2
3	GE	SIGNA EXCITE	N.A.	Sagittal	7	3	900	256 x 256	1.02 x 1.02 x 1.2	8	166	1
3	GE	SIGNA HDxt	N.A.	Sagittal	7	3	900	256 x 256	1.02 x 1.02 x 1.2	8	166	2
3	Phillips	Achieva	TFE	Sagittal	7	3	None	256 x 256	0.98 x 0.98 x 1.2	9	150	4
3	Siemens	Skyra	MPRAGE	Coronal	1380	3	700	256 x 256	0.98 x 0.98 x 1	9	176	2
3	Siemens	Skyra	MPRAGE	Coronal	1400	3	708	256 x 256	0.98 x 0.98 x 1	9	192	1
3	Siemens	Skyra	MPRAGE	Sagittal	2300	3	900	256 x 256	1 x 1 x 1.2	9	176	1
3	Siemens	Trio	MPRAGE	Axial	1620	4	950	192 x 256	0.98 x 0.98 x 1	15	160	1
3	Siemens	Trio Tim	MPRAGE	Sagittal	1310	2	900	256 x 256	0.98 x 0.98 x 1	10	144	1

3	Siemens	Trio Tim	MPRAGE	Sagittal	2300	3	900	240 x 256	1 x 1 x 1.2	9	160	2
3	Siemens	Trio Tim	MPRAGE	Sagittal	2500	3	1100	256 x 256	1 x 1 x 1	7	192	3
3	Siemens	Prisma	MPRAGE GRAPPA	Sagittal	2300	3	900	240 x 256	1.05 x 1.05 x 1.2	9	176	6

T: Tesla; FGE: Fast Gradient Echo; FSPGE: Fast Spoiled Gradient Echo; GRAPPA: Generalized Autocalibrating Partially Parallel Acquisition; MPRAGE: Magnetization Prepared Rapid Gradient Echo; N.A.: Not available; TE: Echo time; TFE: Turbo Field Echo; TI: Inversion time; TR: Repetition time

APPENDIX C - Differences in clinical and cognitive characteristics between patients and healthy controls within each relationship group ($p < 0.05$)

	Opposite-sex				Same-sex			
Characteristic	**HC (n = 20)**	**PT (n = 20)**	***F***	***p***	**HC (n = 20)**	**PT (n = 20)**	***F***	***p***
NPI-Q[a]	0.00 (1.00)	4.00 (7.00)	6.88	0.013	0.0 (0.00)	1.00 (3.00)	12.35	0.001
MMSE/MoCA	29.40 (0.68)	24.60 (4.20)	16.22	<0.001	29.40 (1.05)	24.80 (4.22)	10.01	0.003
SF	39.20 (7.17)	21.37 (8.98)	14.05	0.001	41.05 (6.77)	22.65 (9.26)	22.13	<0.001
TMT-A	24.35 (8.47)	39.53 (14.32)	4.46	0.057	23.70 (7.54)	54.00 (32.97)	3.10	0.088
TMT-B	52.25 (11.03)	130.24 (65.27)	9.66	0.004	53.90 (17.96)	156.94 (86.01)	7.24	0.016
TMT-B-A	27.90 (10.51)	92.47 (60.39)	8.25	0.007	30.20 (14.99)	107.83 (73.75)	5.71	0.023
LMT-IR	17.00 (3.77)	7.32 (4.28)	23.93	<0.001	16.05 (3.73)	8.95 (5.21)	13.31	0.001
LMT-DR	15.74 (4.70)	3.22 (3.67)	40.12	<0.001	14.85 (4.16)	5.05 (5.99)	14.53	0.001
DST-F[a]	7.00 (2.00)	6.00 (3.00)	0.83	0.370	7.00 (2.00)	6.00 (1.00)	0.54	0.467
DST-B[a]	6.00 (2.00)	5.00 (2.00)	0.24	0.628	5.00 (1.00)	4.00 (2.00)	5.36	0.027

Values are mean (standard deviation)

[a] Median (Interquartile range) for variables not normally distributed

DS-F/B: Digit Span Test – forward and backward; HC: Healthy controls; LMT-IR/DR: Logical Memory Test – immediate and delayed recall; MMSE/MoCA: Mini Mental State Examination/Montreal Cognitive Assessment; NPI-Q: Neuropsychiatric Inventory Questionnaire; PT: Patients; SF: Semantic Fluency; TMT-A/B/B-A: Trail Making Test - part A, part B and difference B-A

APPENDIX D - Differences in rates of psychiatric medications between patients and healthy controls within each relationship group ($p < 0.05$)

	Healthy controls				Patients			
Psychiatric medication	**OS (n =20)**	**SS (n =20)**	***χ2***	***p***	**OS (n =20)**	**SS (n =20)**	***χ2***	***p***
Any[a]	5/15	8/12	1.03	0.31	4/16	9/11	2.85	0.09
SNRI[a]	1/19	0/20	1.00	0.32	0/20	2/18	2.05	0.15
SSRI[a]	4/16	7/13	1.13	0.29	2/18	7/13	3.49	0.06
Beta Blockers[a]	1/19	0/20	1.00	0.32	0/20	0/20	0.00	1.00
TCA[a]	0/20	0/20	0.00	1.00	1/19	0/20	1.00	0.32
BDZ[a]	0/20	1/19	1.00	0.32	1/19	1/19	0.00	1.00
AA[a]	0/20	0/20	0.00	1.00	0/20	1/19	1.00	0.32

AA: Atypical antipsychotics; BDZ: Benzodiazepines; SNRI: Serotonin-norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants.

[a] Medicated cases: Yes/No

Table **1** Comparisons (*t* tests) of clinical and cognitive characteristics between individuals in opposite-sex and same-sex relationships within groups of patients and healthy controls ($p < 0.05$)

	Healthy controls				**Patients**			
Variable	**OS (n =20)**	**SS (n =20)**	***t***	***p***	**OS (n =20)**	**SS (n =20)**	***t***	***p***
Age	57.30 (10.86)	58.55 (11.66)	-0.35	0.73	72.50 (9.75)	72.45 (10.84)	0.01	0.99
Education	17.35 (1.81)	17.45 (1.79)	-0.17	0.86	16.60 (2.54)	16.30 (2.30)	0.39	0.70
Sex (F/M)[a]	5/15	6/14	0.12	0.72	10/10	10/10	0.00	1.00
Race[a,b]	18/2/0/0/0	18/0/1/1/0	4.00	0.26	17/2/0/1/3	16/0/0/1/3	5.03	0.17
APOE[a,c]	2/11/5/0/2	1/11/6/0/2	0.42	0.94	1/5/7/4/3	1/5/7/4/3	0.00	1.00
GMF[d,e]	0.48 (0.05)	0.44 (0.07)	-1.35	0.18	0.37 (0.04)	0.38 (0.08)	1.03	0.30
CDR[d,e]	0.00 (0.00)	0.00 (0.00)	1.43	0.60	0.50 (0.50)	0.50 (0.40)	-0.91	0.46
NPI-Q[d,e]	0.90 (2.24)	0.35 (0.59)	0.09	0.95	4.05 (3.90)	3.78 (5.44)	-0.10	0.92
GDS[d,e]	0.00 (1.00)	0.00 (1.00)	0.43	0.73	1.00 (2.00)	2.00 (3.00)	0.52	0.63
MMSE/MoCA	29.40 (0.68)	29.40 (1.05)	0.00	1.00	24.60 (4.20)	24.80 (4.22)	-0.15	0.88
SF	39.20 (7.17)	41.05 (6.77)	-0.79	0.43	21.37 (8.98)	22.65 (9.26)	-0.44	0.66
TMT-A	24.35 (8.47)	23.70 (7.54)	0.26	0.80	39.53 (14.32)	54.00 (32.97)	-1.79	0.08
TMT-B	52.25 (11.03)	53.90 (17.96)	-0.35	0.73	130.24 (65.27)	156.94 (86.01)	-1.03	0.31
TMT-B-A	27.90 (10.51)	30.20 (14.99)	-0.56	0.58	92.47 (60.39)	107.83 (73.75)	-0.67	0.51
LMT-IR	17.00 (3.77)	16.05 (3.73)	0.79	0.43	7.32 (4.28)	8.95 (5.21)	-1.05	0.30
LMT-DR	15.74 (4.70)	14.85 (4.16)	0.62	0.54	3.22 (3.67)	5.05 (5.99)	-1.11	0.27
DST-F[d,e]	7.00 (2.00)	7.00 (2.00)	-0.47	0.66	6.00 (3.00)	6.00 (1.00)	0.18	0.86
DST-B[d,e]	6.00 (2.00)	5.00 (1.00)	-1.11	0.30	5.00 (2.00)	4.00 (2.00)	-0.85	0.41

Values are mean (standard deviation)

[a] Chi-squared

[b] Race: White/Black/Asian/Mixed/Latino

[c] APOE genotypes: ε3ε2/ε3ε3/ε3ε4/ε4ε4/unknown

[d] Median (Interquartile range) for variables not normally distributed

[e] Mann-Whitney *U* test for variables not normally distributed

CDR: Clinical Dementia Rating; DS-F/B: Digit Span Test – forward and backward; GMF: Gray Matter Fraction; LMT-IR/DR: Logical Memory Test – immediate and delayed recall; MMSE/MoCA: Mini Mental State Examination/Montreal Cognitive Assessment; NPI-Q: Neuropsychiatric Inventory Questionnaire; OS: Opposite-sex; SF: Semantic Fluency; SS: Same-sex; TMT-A/B/B-A: Trail Making Test - part A, part B and difference B-A

Table **2** Main effects of Diagnosis and Relationship type (ANCOVA models) on clinical and cognitive characteristics of participant subgroups ($p < 0.05$)

	Diagnosis				**Relationship**			
Variable	**HC (n =20)**	**PT (n =20)**	***F***	***p***	**OS (n =20)**	**SS (n =20)**	***F***	***p***
Age	57.93 (11.14)	72.47 (10.18)	36.31	<0.01	64.90 (12.77)	65.50 (13.15)	0.06	0.80
Education	17.40 (1.78)	16.45 (2.40)	3.96	0.50	16.98 (2.21)	16.88 (2.11)	0.04	0.84
Sex (F/M)[a]	11/29	20/20	4.27	0.04	15/25	16/24	0.05	0.82
Race[a,b]	36/2/1/1/0	33/2/0/2/3	0.74	0.39	35/4/0/1/0	34/0/1/2/3	1.23	0.27
APOE[a,c]	3/22/11/0/4	2/10/14/8/6	13.46	0.01	3/16/12/4/5	2/16/13/4/5	0.24	0.99
GMF[d]	0.44 (0.07)	0.37 (0.05)	49.01	<0.01	0.42 (0.11)	0.42 (0.08)	0.15	0.70
CDR[d]	0.00 (0.50)	0.50 (0.50)	92.85	<0.01	0.25 (0.50)	0.50 (0.50)	0.28	0.60
NPI-Q[d]	0.00 (1.00)	2.00 (7.00)	17.41	<0.01	0.00 (6.00)	1.00 (1.00)	0.27	0.60
GDS[d]	0.00 (1.00)	1.00 (2.00)	5.69	0.02	0.00 (1.00)	2.00 (3.00)	0.17	0.68
MMSE/MoCA	29.40 (0.87)	24.70 (4.16)	34.82	<0.01	27.00 (3.84)	27.10 (3.83)	0.02	0.89
SF	40.17 (6.94)	22.03 (9.02)	56.56	<0.01	30.56 (12.10)	31.85 (12.28)	0.70	0.40
TMT-A	24.03 (7.92)	46.95 (26.35)	12.09	<0.01	31.74 (13.86)	38.85 (28.16)	2.65	0.11
TMT-B	53.08 (14.74)	143.97 (76.73)	21.41	<0.01	88.08 (59.24)	102.71 (79.27)	1.32	0.26
TMT-B-A	29.05 (12.83)	100.37 (67.06)	18.73	<0.01	57.57 (52.38)	66.97 (64.48)	0.63	0.43
LMT-IR	16.51 (3.73)	8.13 (4.78)	44.53	<0.01	12.16 (6.32)	12.59 (5.72)	0.13	0.72
LMT-DR	15.28 (4.40)	4.16 (5.01)	65.45	<0.01	9.65 (7.59)	10.08 (7.09)	0.20	0.66
DST-F[d]	7.00 (2.00)	6.25 (2.00)	4.06	0.05	7.00 (2.00)	6.00 (1.00)	0.03	0.86
DST-B[d]	6.00 (1.00)	4.50 (1.00)	12.32	<0.01	5.50 (2.00)	5.00 (2.00)	1.07	0.30

Values are mean (standard deviation)

[a] Chi-squared

[b] Race: White/Black/Asian/Mixed/Latino

[c] APOE genotypes: ε3ε2/ε3ε3/ε3ε4/ε4ε4/unknown

[d] Median (Interquartile range) for variables not normally distributed

CDR: Clinical Dementia Rating; DS-F/B: Digit Span Test – forward and backward; GDS: Geriatric Depression Scale; GMF: Gray Matter Fraction; HC: Healthy controls; LMT-IR/DR: Logical Memory Test – immediate and delayed recall; MMSE/MoCA: Mini Mental State Examination/Montreal Cognitive Assessment; NPI-Q: Neuropsychiatric Inventory Questionnaire; OS: Opposite-sex; PT: Patients; SF: Semantic Fluency; SS: Same-sex; TMT-A/B/B-A: Trail Making Test - part A, part B and difference B-A

Table **3** Differences in GM regional volumes between healthy controls and patients ($p < 0.05$ FWE)

p-value	Cluster size	Side	Brain region	*t* value	MNI coordinates		
					x	*y*	*z*
All HC > All PT							
< 0.001	66282	L	PHG (BA 34)	6.66	-21	2	-21
		L	MFG (BA 10)	6.10	-3	57	-2
		R	SFG (BA 10)	6.05	24	56	3
0.008	964	R	FG (BA 37)	4.80	-40	-45	-16
		R	MOG (BA 37)	4.23	-48	-68	-10
		R	MOG (BA 39)	3.93	-54	-70	-15
OS-HC > OS-PT							
< 0.001	4535	R	PHG (BA 30)	6.32	24	-36	0
		R	Hippocampus	5.90	32	-8	-21
		R	Hippocampus	5.85	32	-32	-9
< 0.001	3049	L	Amygdala	6.12	-26	-10	-15
		L	Amygdala	5.23	-21	0	-21
		L	PHG (BA 28)	4.73	-21	-24	-12
< 0.001	12367	R	STG (BA 41)	4.81	54	-27	12
		R	Insula (BA 13)	4.78	45	-12	-4
		R	STG (BA 42)	4.30	62	-12	9
SS-HC > SS-PT							
< 0.001	5371	R	SFG (BA 10)	5.87	26	63	-4
		R	SFG (BA 10)	5.42	22	57	3
		L	MFG (BA 11)	5.13	-10	62	-18
< 0.001	2130	L	Cuneus (BA 7)	4.54	-3	-68	30
		R	PCC (BA 23)	4.48	9	-56	16
		L	Precuneus (BA 31)	3.88	-8	-68	14
0.007	963	L	PHG (BA 34)	4.30	-21	2	-21
		L	IFG (BA 47)	4.22	-20	21	-22
		L	PHG (BA 28)	4.19	-16	-14	-12
0.007	962	L	Insula (BA 13)	4.68	-39	-30	14
		L	STG (BA 22)	4.13	-56	-28	2
		L	STG (BA 42)	4.11	-46	-28	10

BA: Brodmann area; FG: Fusiform gyrus; GM: Grey matter; HC: Healthy controls; IFG: Inferior frontal gyrus; MFG: Medial frontal gyrus; MOG: Middle occipital gyrus; PCC: Posterior cingulate cortex; PHG: Parahippocampal gyrus; PT: Patients; OS: Opposite-sex; SFG: Superior frontal gyrus; SS: Same-sex; STG: Superior temporal gyrus

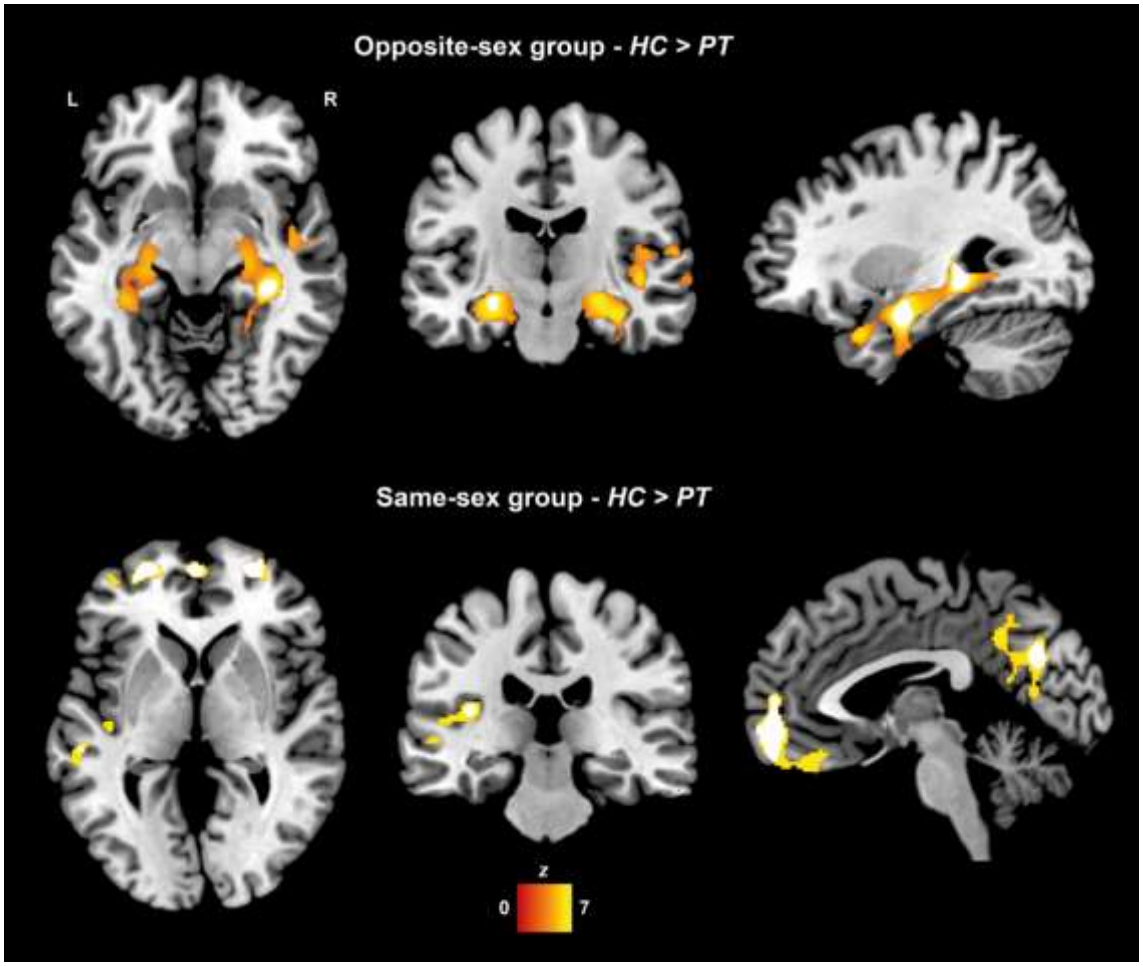

Figure 1