Cognitive impairment and depression: Meta-analysis of structural magnetic resonance imaging studies

Lenka Zacková a,b,*, Martin Jáni a,c, Milan Brázdiil a,b, Yuliya S. Nikolova d, Klára Marečková a,d

a) Brain and Mind Research Programme, Central European Institute of Technology, Masaryk University (CEITEC MU), 5 Kamenice, Brno 62500, Czech Republic
b) Department of Neurology, St. Anne’s University Hospital and Faculty of Medicine, Masaryk University, 664/53 Pekarska, Brno 65691, Czech Republic
c) Department of Psychiatry, Faculty of Medicine, Masaryk University and University Hospital Brno, Jihlávská 20, Brno 62500, Czech Republic
d) Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON MST 1H8, Canada

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A B S T R A C T
Longitudinal comorbidity of depression and cognitive impairment has been reported by number of epidemiological studies but the underlying mechanisms explaining the link between affective problems and cognitive decline are not very well understood. Imaging studies have typically investigated patients with major depressive disorder (MDD) and mild cognitive impairment (MCI) separately and thus have not identified a structural brain signature common to these conditions that may illuminate potentially targetable shared biological mechanisms. We performed a meta-analysis of 48 voxel-based morphometry (VBM) studies of individuals with MDD, MCI, and age-matched controls and demonstrated that MDD and MCI patients had shared volumetric reductions in a number of regions including the insula, superior temporal gyrus (STG), inferior frontal gyrus, amygdala, hippocampus, and thalamus. We suggest that the shared volumetric reductions in the insula and STG might reflect communication deficits and infrequent participation in mentally or socially stimulating activities, which have been described as risk factors for both MCI and MDD. We also suggest that the disease-specific structural changes might reflect the disease-specific symptoms such as poor integration of emotional information, feelings of helplessness and worthlessness, and anhedonia in MDD. These findings could contribute to better understanding of the origins of MDD-MCI comorbidity and facilitate development of early interventions.

1. Introduction

Major depressive disorder (MDD), a heterogeneous neuropsychiatric disorder associated with abnormalities in psychomotor, cognitive and affective functioning, is the leading cause of disability worldwide and a major contributor to the overall global burden of disease (Bonekamp et al., 2010). Longitudinal studies revealed that, compared to healthy controls, MDD patients have higher risk of mild cognitive impairment (MCI), the transitional stage between normal cognitive aging and dementia, characterized by slight impairment in cognitive functioning but preserved ability to function in daily life (Bartels et al., 2018; Becker et al., 2009; Cervilla et al., 2006; Hébert Réjean et al., 2000; Jacob et al., 2017; Khedr et al., 2009; Lindsay et al., 2002; Muller et al., 2007; Ng et al., 2009; Paillard-Borg et al., 2009; Panza et al., 2008; Saczynski et al., 2010). Data from Cardiovascular Health Study demonstrated that severity of depressive symptoms predicted diagnosis of MCI 6 years later (Burke & Barnes, 2006). Further research showed that history of depression approximately doubled one’s risk of subsequent dementia in general (Jorm, 2001) and Alzheimer disease in particular (Ownby et al., 2006). A recent behavioral meta-analysis by Chan et al (2019) supported this higher risk of dementia in MDD patients vs. a control group and pointed out that this effect was particularly pronounced in those who did not use anti-depressant medication. Consistently, patients with MCI or dementia had higher risk of depression than healthy controls (Juang et al., 2011; Mizra et al., 2017).

Literature suggests that affective problems over the life course might be associated with a decline in cognitive state even prior to the onset of cognitive impairment. While some studies did not find any relationship between affective problems and decline in cognitive state (Ganguli, 2006; Bunce et al., 2012; Gale et al., 2013; Brailean et al., 2017), a

* Corresponding author at: Department of Neurology, St. Anne’s University Hospital and Faculty of Medicine, Masaryk University, 664/53 Pekarska, Brno, 65691, Czech Republic.
E-mail address: l.zackova10@gmail.com (L. Zacková).

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majority of studies found such significant associations (Geerlings et al., 2000; Paterniti et al., 2002; Kohler et al., 2016; Johnson et al., 2013; Royall & Palmer, 2013; Rajan et al., 2014; Gulpers et al., 2016) and it has been proposed that affective problems might be related to accelerated cognitive aging (da Silva et al., 2013; Gulpers et al., 2016). Moreover, a recent systematic review of 34 longitudinal studies focused on the link between depression and decline in cognitive function such as memory loss, executive function and information processing speed over time and found that people with depression experienced a greater decline in cognitive state in older adulthood than those without depression (John et al., 2018). Symptoms of cognitive impairment, including worse memory, psychomotor speed, attention, visual learning as well as worse executive functioning, were observed also in patients in the first episode of depression (Roca et al., 2015; Rock et al., 2014). The largest effects were present in attention and executive function and these symptoms persisted also during remission when subjects did not experience mood problems but their performance still differed from that of healthy controls (Roca et al, 2015; Rock et al, 2014).

While the epidemiological evidence of the longitudinal comorbidity of depression and cognitive impairment described above is well established, the underlying mechanisms explaining the link between affective problems and cognitive decline are not very well understood (da Silva et al., 2013). According to Butters et al. (2008), depression-associated cerebrovascular disease and glucocorticoid neurotoxicity may lead to lower cognitive reserve and contribute to accelerated cognitive decline. It has been suggested that alterations in brain-derived neurotrophic factor (BDNF) and somatostatin (SST), signalling neuropetides important for neuronal survival and function, and BDNF-related genes might contribute to the comorbidity between depression and age-related disorders (Sibille, 2013). However, it is unclear how these purported mechanisms may translate into unique and overlapping macrostructural abnormalities associated with MDD and age-related cognitive impairment.

Imaging studies have typically examined major depressive disorder (MDD) (Gray et al., 2020; Li et al., 2020a; Li et al., 2020b) and mild cognitive impairment (MCI) (Qin et al., 2020; Xu et al., 2020) separately and/or in small samples and thus were not able to identify a structural brain signature common to these conditions that may illuminate potentially targetable shared biological mechanisms. To fill this gap, we performed a meta-analysis of structural brain imaging studies of individuals with MDD, MCI, and their respective age-matched controls to identify neural correlates which are shared between MDD and MCI. We also aimed to identify the disease-specific neural correlates and discuss how these shared and unique neural correlates might reflect the comorbidity of these disorders and the disease-specific symptomatology, respectively. Based on the research by Rayner et al (2016), which suggested that decreased grey matter volume in hippocampus and prefrontal cortex might lead to cognitive dysfunction in depression, we hypothesized that both MCI and MDD patients might show lower grey matter volume (GMV) in these areas than healthy controls.

2. Materials and methods

Our study was carried out in compliance with Items for systematic reviews and meta-analyses (PRISMA), an evidence-based minimum set of items for reporting in meta-analysis (Moher, 2009).

2.1. Study selection

An initial search in the Web of Science and PubMed databases was done on 1.2.2020 using the following query: (((depress* OR MDD) OR (“MCI” OR “mild cognitive impairment”)) AND (VBM OR MRI OR GM OR “grey matter volume”)). This search returned 10 054 English articles in the Web of Science database and 10 017 English articles in the PubMed database. After removing duplicates, we screened the titles and abstracts of all remaining studies and identified 561 relevant research articles (see Fig. 1). These 561 research articles were assessed by the first author as well as two additional independent co-workers for the following inclusion criteria: (1) studies in English language, (2) studies in adult humans diagnosed with either MDD or MCI (but without a comorbidity) compared with age-matched healthy controls, (3) voxel-based morphometry (VBM) and (4) whole brain analysis reporting peaks in the Montreal Neurological Institute (MNI) or Talairach stereotactic space (TAL). In the case of unclear articles, there was always a mutual consultation followed by a subsequent decision on the relevance of the article. In case of missing data, we contacted the relevant authors via email and if we did not receive necessary information, we excluded those articles as inappropriate. All inclusion criteria were met by a total of 48 articles which we included in the meta-analysis (see Fig. 1).

Characteristics of these 48 studies MDD (n = 37) and MCI (n = 11) are provided in Tables 1 and 2, respectively.

2.2. Meta-analytic neuroimaging methods

The meta-analysis was conducted using SDM-PSI (Seed-based d Mapping with Permutation of Subject Images) software, version 6.21 (Albajas-Eizagirre et al., 2019b; Radua et al., 2012). The method description and tutorial have been previously published (Albajas-Eizagirre et al., 2019a; Albajas-Eizagirre et al., 2019b) and it is also available online (www.sdmproject.com). In short, SDM-PSI uses reported peak coordinates and t values as an input to generate multiple imputations of study images. The SDM-PSI then performs subject-based permutation testing to create (1) a map of effect sizes (Hedge’s g) with positive and negative differences and (2) a map of variance, derived from the effect sizes and the sample sizes in the study. The exact effect size is calculated only in voxels containing a peak; the effect size for the remaining voxels is estimated depending on the distance to close peaks by means of an unnormalised Gaussian kernel. Finally, subject images are imputed for each study, followed by subject-based standard permutation test, which allows the use of standard voxel-wise tests. We used the recommended Gaussian kernel with the full width at half maximum (FWHM) of 20 mm and 2 mm voxel size, which provides the optimal balance between sensitivity and specificity (Radua et al., 2012). For the permutation parameters, we applied default 50 imputations of study images and 1000 permutation of subject images for each study (Albajas-Eizagirre et al., 2019b).

We conducted two separate mean analyses, one for MDD vs healthy controls (HC) contrast and second for MCI vs HC contrast, each with age as a covariate. We applied voxel-level (height) threshold of p < 0.025 (0.05/2 for both positive and negative contrasts) with threshold-free cluster enhancement (TFCE) for multiple comparisons and a minimal cluster extent of 10 voxels and a cluster-level (extent) threshold of 10 voxels. All results are reported in MNI coordinate system.

2.3. Overlap analyses

We computed overlap between results of the two mean analyses (MDD and MCI) with SDM-PSI multimodal meta-analysis utility (Radua et al., 2012). This method allows the original p-values of individual meta-analyses to be estimated with some degree of error and can eventually show results in regions that were close to significance which gives a more realistic approximation than simple overlap.

2.4. Complementary analyses

Heterogeneity analysis was used to assess which brain regions found by our mean analysis showed unexplained variability across the studies. SDM calculates Q statistic based on effect-size variance between studies in a given area. The heterogeneity is tested for significance by determining if the observed between-study variance for a given area is greater than the variance resulting from sampling error alone. The heterogeneity values are reported as standard z values in SDM, presented.
The potential bias was assessed by Egger tests (Sterne and Egger, 2001) reported in Supplementary Table 1S.

To investigate confound of medication we repeated the analysis with subset of MDD studies which included only medication free patients (n = 15). Therefore, we conducted mean analysis for medication free MDD vs HC contrast and subsequently we computed the overlap of medication free MDD and MCI mean analyses. Detailed results of analysis with medication free subset are reported in Supplementary Tables 2S and 3S.

3. Results

3.1. MDD patients vs. Healthy controls

The contrast between the MDD group (n = 1364) and HC (n = 1464) showed volumetric reductions in frontal, temporal, parietal as well as occipital regions (see Fig. 2). In particular, lower volume was found in an extensive cluster with peak in left striatum, but extending to other subcortical structures (right striatum and hippocampus), anterior and middle cingulate cortex, insula, frontal, temporal and occipital gyr. Decreased volume in MDD was also found in a cluster extending to left superior temporal lobe, insula and inferior frontal gyrus and in another cluster extending to left inferior parietal lob and supramarginal gyrus. Remaining smaller clusters with reduced volume in MDD were found in left cerebellum, fusiform gyrus, postcentral gyrus and left and right middle frontal gyri. Detailed description of these volumetric reductions in MDD as well as statistics are provided in Table 3A. There were no regions with larger volume in the MDD vs. control group. The Egger test was not significant for any of the clusters, suggesting no detectable publication bias.

3.2. MCI patients vs. Healthy controls

The contrast between the MCI group (n = 407) and healthy controls (n = 392) showed reduced volume in a single cluster which included right insula, rolandic operculum and superior temporal lobe. Detailed description of volumetric reductions in MCI as well as statistics are provided in Table 3B. There were no regions with larger volume in the MCI vs. control group. The Egger test was not significant for the single cluster, suggesting no detectable publication bias.

3.3. Overlap analysis

Multimodal meta-analysis of overlapping volume reductions in MDD and MCI identified 3 clusters. The most extensive cluster included right hemisphere insula, middle and superior temporal gyrus, temporal pole, inferior frontal gyrus, amygdala, hippocampus, and parahippocampal gyrus. Smaller cluster in left hemisphere included insula, superior temporal gyrus, temporal pole and inferior frontal gyrus. Finally, the smallest cluster included left thalamus (see Fig. 2). Detailed description and the relevant statistics are provided in Table 3C.

Fig. 1. PRISMA flow diagram representing selection procedure in meta-analysis
4. Discussion

We performed a meta-analysis of 48 voxel-based morphometry (VBM) studies of major depressive disorder (MDD), mild cognitive impairment (MCI), and their respective age-matched controls, and demonstrated that MDD and MCI patients had shared volumetric reductions in number of regions including the insula, superior temporal gyrus, inferior frontal gyrus, amygdala, hippocampus, and thalamus. We suggest that these shared volumetric decreases might, in part, explain the epidemiological evidence of the longitudinal comorbidity between MDD and MCI (Roca et al., 2015; Rock et al., 2014; Chan et al., 2019; Huang et al., 2011; Mirza et al., 2017; Ismail et al., 2017) and that the

### Table 1
Characteristics of the 37 MDD studies included in meta-analysis

| Study               | n  | Age   | HAMD  | Duration of illness | Medication |
|---------------------|----|-------|-------|---------------------|------------|
|                     | MDD| HC    | MDD   | HC                  | Months     |
| Amico et al. (2011) | 33 | 64    | 32.0  | 30.4                | 23.0       |
| Arnene et al. (2013)| 39 | 66    | 36.3  | 32.1                | NA         |
| Cai et al. (2015)   | 23 | 23    | 30.0  | 28.2                | 29.7       |
| Egger et al. (2008) | 14 | 20    | 71.4  | 72.3                | NA         |
| Grieve et al. (2013)| 102| 34    | 33.8  | 31.5                | 21.0       |
| Guo et al. (2014)   | 44 | 44    | 27.52 | 29.39               | 25.18      |
| Hardada et al. (2018)| 16 | 30    | 56    | 58                  | 20         |
| Hwang (2010)        | 43 | 26    | 79.6  | 79.5                | 29.4       |
| Chen et al. (2016)  | 27 | 28    | 33    | 33                  | 22         |
| Igata et al. (2017) | 39 | 42    | 45.8  | 41.2                | 21.8       |
| Kim et al. (2020)   | 22 | 25    | 38.5  | 35.3                | 24.48      |
| Kong et al. (2013)  | 29 | 33    | 30.01 | 29.91               | 28.63      |
| Lai (2013)          | 38 | 27    | 36.57 | 38.29               | 22.26      |
| Li et al. (2010)    | 25 | 25    | 46.5  | 46.6                | 21.9       |
| Liu et al. (2019)   | 21 | 30    | 34.14 | 33.43               | 24.48      |
| Machino et al. (2014)| 29| 29    | 39.57 | 38.66               | 13.90      |
| Mwangi et al. (2012a)| 15| 16    | 46.1  | 40.6                | 23.2       |
| Mwangi et al. (2012b)| 15| 14    | 44.7  | 43.0                | 27.87      |
| Nakano et al. (2014)| 36| 54    | 49.0  | 45.4                | 15.4       |
| Opel et al. (2016)  | 20 | 20    | 37.9  | 36.3                | 22.2       |
| Peng et al. (2011)  | 22 | 30    | 46.7  | 45.9                | 18.5       |
| Salvador et al. (2011)| 58| 107   | 38.8  | 36.2                | NA         |
| Shen et al. (2010)  | 147| 130  | 30.58 | 30.09               | 23.83      |
| Scheuerecker et al. (2010)| 13| 15   | 37.9  | 35.5                | 20.5       |
| Smith et al. (2009) | 16 | 13    | 65.3  | 67.4                | 26.0       |
| Stratmann et al. (2014)| 132| 132  | 37.9  | 37.9                | 20.48      |
| Tang et al. (2007)  | 14 | 13    | 29.5  | 29.46               | NA         |
| Vasic et al. (2008) | 15 | 14    | 37.4  | 31.4                | 16.9       |
| Wagner et al. (2008)| 15 | 16    | 41.4  | 38.8                | 7.5        |
| Xie et al. (2012)   | 18 | 25    | 68.61 | 74.28               | NA         |
| Yang (2015)         | 50 | 50    | 31.12 | 31.30               | 23.10      |
| Yang et al. (2017)  | 82 | 82    | 28.85 | 27.72               | 23.11      |
| Zhang (2009)        | 15 | 15    | 33.5  | 33.4                | 21.1       |
| Zhang et al. (2012) | 33 | 32    | 20.52 | 21.03               | 25.35      |
| Zou et al. (2010)   | 23 | 23    | 31.1  | 36.6                | 24.4       |
| Mean/Summary        | 36.1| 39.0 | 40.9  | 39.7                | 22.9       |
| W mean by n         | 38.4| 37.8 | 37.8  | 22.8                | 56.6       |
| W mean by age       | 33.8| 36.8 | 22.9  | 54.8                |

MDD: Major Depressive Disorder; HC: Healthy Controls; HAMD: Hamilton Rating Scale for Depression; W: weighted.

### Table 2
Characteristics of the 11 MCI studies included in meta-analysis

| Study              | n  | Age   | MMSE  | Threshold |
|--------------------|----|-------|-------|-----------|
|                    | MCI| HC    | MCI   | HC        |
| Barberau (2008)    | 28 | 28    | 69.3  | 63.3      |
| Bonekamp (2010)    | 10 | 20    | 72.7  | 75.3      |
| Duarte et al. (2006)| 32| 14    | 74.1  | 69.5      |
| Han (2012)         | 17 | 18    | 69.7  | 66.5      |
| Minciu et al. (2019)| 20| 14    | 74.75 | 68.64     |
| Novellino et al. (2019)| 55| 49    | 74.1  | 71.6      |
| Pennamen (2005)    | 51 | 32    | 72    | 74        |
| Son et al. (2013)  | 31 | 50    | 75.0  | 77.2      |
| Xie et al. (2012)  | 17 | 25    | 75.12 | 74.28     |
| Yin et al. (2014)  | 11 | 22    | 66.6  | 62.1      |
| Zhang et al. (2012)| 74 | 120   | 78.2  | 77.6      |
| Mean/Summary       | 31.5| 35.6 | 72.9  | 70.6      |
| W mean by n        | 73.9| 73.2 | 25.3  | 28.2      |
| W mean by age       | 31.9| 36.8 | 25.5  | 28.5      |

MCI: Mild Cognitive Impairment; HC: Healthy Controls; MMSE: Mini-Mental State Examination; W: weighted.
consistent with previous findings in the respective groups of patients. (Lisman et al., 2017), and the thalamus, which relays information be
for both MCI and MDD (Sliz et al., 2012). These deficits in engaging in mentally or socially stimulating activities, which have been described as risk factors
cognition studies across 30 clinical conditions including both psychiatric
diseases. We found VBM differences between MDD patients and healthy controls
meta-analysis of social cognitive
to a meta-analysis of social cognition studies across 30 clinical conditions including both psychiatric and neurological disorders, which concluded that social cognitive

| Peak region       | BA                  | SDM-Z             | Voles   | MNI coordinates | cluster breakdown              |
|-------------------|---------------------|-------------------|---------|-----------------|--------------------------------|
|                   | Hedge's g           | Variance          | HQ²     | x               | y     | z     |                      |
| L. striatum       | 8, 9, 10, 11, 20, 21, 22, 24, 25, 28, 30, 32, 34, 35, 37, 38, 42, 45, 46, 47, 48 | –7 398 | 0,003 | –1,78 | 13,744 | 36   | 22   | –4 |
|                   |                     |                   |         | L & R striatum  | L & R thalamus                 |
|                   |                     |                   |         |                  | L & R ant. cing./paracing. g.  |
|                   |                     |                   |         |                  | L & R med. cing./paracing. g.  |
|                   |                     |                   |         |                  | L & R g. rectus                 |
|                   |                     |                   |         |                  | l. caudate nucleus              |
|                   |                     |                   |         |                  | L. supr. motor area             |
|                   |                     |                   |         |                  | L. olfactory cortex             |
|                   |                     |                   |         |                  | R hippocampus                   |
|                   |                     |                   |         |                  | R parahippocampal g.            |
|                   |                     |                   |         |                  | R insula                        |
|                   |                     |                   |         |                  | R inf. fron. g., orbital part   |
|                   |                     |                   |         |                  | R mid. fron. g.                 |
|                   |                     |                   |         |                  | L & R sup. fron. g., medial     |
|                   |                     |                   |         |                  | R sup. fron. g., dorsolateral   |
|                   |                     |                   |         |                  | R.rolandic operculum            |
|                   |                     |                   |         |                  | R sup. temp. g. & temp. pole    |
|                   |                     |                   |         |                  | R fusiform g.                   |
|                   |                     |                   |         | L. sup. temp. g. & temp. pole |
|                   |                     |                   |         | L. insula         | L. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         | L inf. par. (excl. supram. ang.) g. |
|                   |                     |                   |         | L sup. par. g.    | L. cerebellum, lobule VIII, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
| L. temp. pole      | 6, 20, 21, 22, 28, 34, 37, 38, 41, 42, 44, 45, 46, 47, 48 | –8 187  | 0,003 | –2,16 | 5567  | –46  | 14   | 0  |
|                   |                     |                   |         | L. mid. front. g. | L. sup. temp. g. & temp. pole |
|                   |                     |                   |         |                  | L. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         |                  | L inf. par. (excl. supram. ang.) g. |
|                   |                     |                   |         |                  | L sup. par. g.                  |
|                   |                     |                   |         |                  | L. cerebellum, lobule VIII, VIIb, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
|                   |                     |                   |         | L. cerebellum, crus II |
| L. inf. par. g.   | 7, 19, 39, 40       | –8 389  | 0,002 | –2,13 | 1452  | –28  | –72  | 42 |
|                   |                     |                   |         | L. mid. front. g. | L. sup. temp. g. & temp. pole |
|                   |                     |                   |         |                  | L. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         |                  | L inf. par. (excl. supram. ang.) g. |
|                   |                     |                   |         |                  | L sup. par. g.                  |
|                   |                     |                   |         |                  | L. cerebellum, lobule VIII, VIIb, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
|                   |                     |                   |         | L. cerebellum, crus II |
| L. cerebellum,    | N/A                 | –6 553  | 0,002 | –1,34 | 584   | –18  | –70  | –46|
| lobule VIII       |                     |                   |         | L. mid. front. g. | L. sup. temp. g. & temp. pole |
|                   |                     |                   |         |                  | L. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         |                  | L inf. par. (excl. supram. ang.) g. |
|                   |                     |                   |         |                  | L sup. par. g.                  |
|                   |                     |                   |         |                  | L. cerebellum, lobule VIII, VIIb, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
|                   |                     |                   |         | L. cerebellum, crus II |
| L. mid. front. g. | 9, 46               | –6 545  | 0,003 | –2,05 | 359   | –28  | 46   | 28 |
|                   |                     |                   |         | L. mid. front. g. | L. sup. temp. g. & temp. pole |
|                   |                     |                   |         |                  | L. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         |                  | L inf. par. (excl. supram. ang.) g. |
|                   |                     |                   |         |                  | L sup. par. g.                  |
|                   |                     |                   |         |                  | L. cerebellum, lobule VIII, VIIb, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
|                   |                     |                   |         | L. cerebellum, crus II |
| L. postcentral g. | 4, 6                | –6 062  | 0,003 | –1,83 | 122   | –50  | –10  | 46 |
|                   |                     |                   |         | L. postcentral g. | L. sup. temp. g. & temp. pole |
|                   |                     |                   |         |                  | L. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         |                  | L inf. par. (excl. supram. ang.) g. |
|                   |                     |                   |         |                  | L sup. par. g.                  |
|                   |                     |                   |         |                  | L. cerebellum, lobule VIII, VIIb, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
|                   |                     |                   |         | L. cerebellum, crus II |
| L. fusiform g.    | 20                  | –5 960  | 0,003 | –1,39 | 130   | –38  | –26  | –28 |
|                   |                     |                   |         | L. mid. front. g. | L. sup. temp. g. & temp. pole |
|                   |                     |                   |         |                  | L. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         |                  | L inf. par. (excl. supram. ang.) g. |
|                   |                     |                   |         |                  | L sup. par. g.                  |
|                   |                     |                   |         |                  | L. cerebellum, lobule VIII, VIIb, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
|                   |                     |                   |         | L. cerebellum, crus II |
| R mid. front. g.  | 10                  | –4 393  | 0,002 | –1,29 | 16    | 30   | 58   | 4  |
|                   |                     |                   |         | R. mid. front. g. | R. sup. temp. g. & temp. pole |
|                   |                     |                   |         |                  | R. inf. front. g., orbital &    |
|                   |                     |                   |         |                  | triangular part                 |
|                   |                     |                   |         |                  | L sup. par. g.                  |
|                   |                     |                   |         |                  | L. cerebellum, lobule VIII, VIIb, IX |
|                   |                     |                   |         |                  | L cerebellum, crus II           |
|                   |                     |                   |         | L. cerebellum, crus II |

Abbreviations: BA = Brodmann area, SDM-Z = Signed differentiat map Z score, HQ² = heterogeneity Z value, MDD = Major depressive disorder, HC = Healthy controls, R = right, L = Left.

| Peak region       | BA                  | SDM-Z             | Voles   | MNI coordinates | cluster breakdown              |
|-------------------|---------------------|-------------------|---------|-----------------|--------------------------------|
|                   | Hedge's g           | Variance          | HQ²     | x               | y     | z     |                      |
| R insula          | 48, 44, 38, 6       | –4 860  | 0,040 | –1,90 | 878   | 52   | 6    | 16 |
|                   |                     |                   |         | R insula         | R. rolandic operculum            |
|                   |                     |                   |         |                  | R sup. temp. g. & temp. pole    |

Abbreviations: BA = Brodmann area, SDM-Z = Signed differentiat map Z score, HQ² = heterogeneity Z value, MDD = Major depressive disorder, HC = Healthy controls, R = right, L = Left, B = Bilateral.
dysfunction might be a shared transdiagnostic issue (Cotter et al., 2018).

The disease-specific structural changes might then reflect the disease-specific symptoms. For example, the MDD-specific reductions in volume of frontal regions might reflect poor integration of emotional information (Cai et al., 2015) and feelings of helplessness and worthlessness (Yang et al., 2015). Smaller volume of the striatum, which is a key structure for reward processing (Baez-Mendoza & Schultz), might reflect the MDD-specific symptoms of anhedonia. While the MDD-specific reductions were relatively widespread, the MCI-specific reductions were much more focal, located primarily in the insula and rolandic operculum, and thus possibly reflecting more pronounced deficits in cognition and executive function (Goodkind et al., 2015) and deficits in interoceptive awareness and bodily self-consciousness (Blefari et al., 2017), respectively.

MCI is defined as greater than normal age-related changes in cognition (Murman, 2015) and recent research demonstrated that brains of MCI patients are 3 years older than the brains of healthy controls (Kaufmann et al., 2018). Worse cognition (Lam et al., 2014) and older structural brain age relative to chronological age, ranging from +0.8 to +4 years (Koutsouleris et al., 2014; Kaufmann et al., 2018; Han et al., 2018; Han et al., 2012), were also reported in depression. The hypothesis of accelerated aging in depression has been investigated also at the molecular level (Sibille, 2013; Rozycka & Liguz-Lecznar, 2017). MDD patients were found to have shorter telomeres (Squassina et al., 2019), age-dependent changes in gene function (Han et al., 2018), accelerated age-dependent changes in DNA methylation (Han et al., 2018), or raised and dysregulated levels of proteins characteristic for cellular aging (Diniz et al., 2017). Future research might test whether the comorbidity

Fig. 2. Regions of GM volume decreases underlying MDD and MCI symptomatology. Shared regions are depicted in green, MDD-specific regions in blue, and MCI-specific regions in yellow. (R: right; L: left; HC: healthy controls; MCI: mild cognitive impairment; MDD: major depressive disorder; g: gyrus; Voxel-wise threshold p < 0.005 uncorrected; minimum cluster extent 10 voxels, except for multimodal meta-analysis (p < 0.0025))
of MDD and MCI might be explained by accelerated aging. Future research might also collect longitudinal data to study these changes over time.

The possible impact of sex on the alterations in gray matter volume could not be assessed based on the information provided in these 48 structural magnetic resonance studies and should be considered in future research. Given the currently available literature, we were also not able to compare the MCI patients with and without depression to MDD patients without cognitive impairment and normal controls. Further, given the fact that we performed a meta-analysis of cross-sectional studies, we are not able to determine whether active engagement in mentally and socially stimulating activities is the cause of atrophy in the insula and STG or whether the atrophy occurs first and results in the lesser engagement in these activities. It is also important to note that while healthy controls were age-matched with the MDD and MCI patients, the mean age of MDD patients was younger than that of MCI patients. To correct for this difference in age, our analyses used age as a covariate. Still, due to the design of our study, there is a possibility that age might have influenced the shared decreases in GM volume between the MDD and MCI patients and their controls. Finally, the MCI group was considerably smaller than the MDD group and thus the reliability of MCI results might be limited.

Despite these limitations, our meta-analysis of 48 structural magnetic resonance imaging studies suggests that the shared volumetric decreases might, at least in part, underlie the comorbidity of mild cognitive impairment and depression. Considering the rapid demographic aging occurring in populations worldwide, the number of people struggling with comorbid MDD-MCI is likely to increase, and thus early intervention is needed. The number of people struggling with MDD and MCI is likely to increase, and thus early intervention is needed.

Table 3C

Meta-analytic results – Shared volumetric decreases underlying MDD and MCI symptomatology

| Peak region         | BA    | MCI < HC SDM-Z variance | MCI < HC HQ² | MDD < HC SDM-Z variance | MDD < HC HQ² | voxels | MNI | cluster breakdown |
|---------------------|-------|--------------------------|-------------|--------------------------|-------------|--------|-----|-------------------|
| R inf. front. g.,   | 6, 20, 21, 22, 28, 34, 35, 36, 38, 44, 48 | -4.31 0.045 | -0.92 | -4.16 0.003 | -1.13 | 3199 | 54 10 8 | R insula |
| opercular part      |       |                         |             |                          |             |        |     | R mid. temp. g.   |
|                     |       |                         |             |                          |             |        |     | R temp. pole, sup. & mid. temp. g. |
|                     |       |                         |             |                          |             |        |     | R heschl g.       |
|                     |       |                         |             |                          |             |        |     | R inf. front. g., opercular part |
|                     |       |                         |             |                          |             |        |     | R rolandic operculum |
|                     |       |                         |             |                          |             |        |     | R hippocampus      |
|                     |       |                         |             |                          |             |        |     | R parahippocampal g. |
|                     |       |                         |             |                          |             |        |     | R amygdala         |
|                     |       |                         |             |                          |             |        |     | R lenticular nucleus, putamen |
|                     |       |                         |             |                          |             |        |     | R striatum         |
| L inf. front. g.,   | 38, 47, 48 | -2.80 0.045 | -2.88 | -3.66 0.003 | -1.98 | 900  | -40 16 -14 | L insula |
| orbital part        |       |                         |             |                          |             |        |     | L temp. pole, sup. temp. g. |
|                     |       |                         |             |                          |             |        |     | L inf. front. g., orbital part & opercular part |
|                     |       |                         |             |                          |             |        |     | L rolandic operculum |
| L thalamus          |       | -3.27 0.042 | -0.99 | -5.06 0.003 | -0.44 | 138  | -8 -14 | L thalamus |

Abbreviations: BA = Brodmann area, SDM-Z = Signed differentiat map Z score, HQ² = heterogeneity Z value, MCI = Mild cognitive disorder, MDD = Major depressive disorder, HC = Healthy controls, R = right, L = Left, B = Bilateral.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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