Neural Correlates of Apathy in Mild Cognitive Impairment (MCI): a resting state fMRI study

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Abstract

Mild Cognitive Impairment (MCI) is the presence of cognitive decline that is not severe enough for the diagnosis of dementia. Patients that suffer from MCI exhibit many neuropsychiatric symptoms including apathy. Apathy is seen as a state of indifference and patients show diminished voluntary goal-directed behaviour. Apathy could increase the risk of developing MCI in normal cognitive subjects. Moreover, also the progression from MCI to Alzheimer's Disease (AD) could be predicted by apathy. It has been found that MCI, but also the cognitive and executive function deficits that are seen in MCI patients, is associated with altered functional connectivity (FC) patterns. These FC networks can be investigated with resting state (RS) fMRI. The relationship between FC patterns in aMCI with apathy has not been evaluated before. Therefore, the aim of this study was to analyse resting state (rs) fMRI data to investigate the neural correlates of apathy in aMCI.

Rs fMRI was assessed in 31 aMCI patients and twenty healthy controls. Rs fMRI data was analyzed using independent component analysis (ICA). Components of interest were selected for further analysis. We classified two components as default mode network (DMN), one as basal ganglia network (BGN), two as central executive network (CEN) and three/four as the salience network (SN).

We found altered within-network functional connectivity in CEN and SN in MCI patients compared with healthy controls (HCs). Besides, apathy levels in aMCI were correlated with increasing functional connectivity patterns in BGN and SN, whereas apathy levels in aMCI were correlated with decreasing functional connectivity patterns in BGN, CEN and SN. Regarding between-network functional connectivity, weaker connectivity patterns were found between SN and DMN in MCI subjects compared with HCs. Moreover, a negative correlation between level of apathy in MCI patients and connectivity between two components of the SN was found, whereas a positive correlation was found between apathy level and connectivity between the SN and DMN.

The results on alterations in FC in SN and CEN in aMCI patients could be explained by the cognitive deficits in aMCI. Nevertheless, according to the functions of the DMN and the cognitive deficits in aMCI we expected to find more alterations in DMN connectivity in aMCI. Furthermore, altered connectivity in CEN, SN, BGN correlated to apathy could be explained by the presence of apathy in these subjects. Still, more research is needed to elucidate the role of these FC patterns in the development of apathy and the progression of MCI.

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Introduction

Mild Cognitive Impairment

With the population aging, interest is growing concerning the topic of a boundary between normal ageing and dementia, or more specifically Alzheimer's Disease (AD). A transitional state is often called mild cognitive impairment (MCI), incipient dementia or isolated memory impairment. Actually, these terms evolved when patients with impairments in cognition were observed that did not meet the criteria for dementia. In other words, MCI refers to the presence of cognitive decline not severe enough for the diagnosis of dementia (Robert et al., 2006). Broadly, MCI can be divided into two subgroups of which the most common type is amnestic MCI (aMCI). The typical aMCI patient shows a decline in memory function, but other cognitive domains are relatively intact and is not restricted in normal activities of daily living (Petersen, 2004)(Petersen et al., 1999). On the other hand, a less common MCI type (non-amnestic (na)MCI) is characterized by impairments in multiple domains except memory. The prevalence of MCI in adults older than 65 years ranges from 3% to 19% (Gauthier et al., 2006). Some of these MCI patients remain stable or return to normal over time, whereas more than half of them progress to dementia within five years (Gauthier et al., 2006). In particular, aMCI patients have a greater risk of progression to a more advanced stage of AD than naMCI patients (Gauthier et al., 2006).

Apathy

In addition to an impairment in cognitive performances, many MCI patients exhibit neuropsychiatric symptoms. These symptoms might be caused by cognitive decline and could lead to loss of functional abilities (Robert et al., 2006). One of the earliest and most common neuropsychiatric symptoms in MCI and AD, seen in 50% to 70% of the individuals, is apathy (Malloy & Boyle, 2005). Apathy has been defined as diminished voluntary goal-directed behaviour (Levy & Dubois, 2006), characterized by for example loss of interest, lack of motivation and a lack of purpose or meaning in their life (Guercio et al, 2015). In addition, apathy is seen as a state of indifference or the suppression of emotions such as motivation and passion (Monastero, et al., 2009). Moreover, social withdrawal is often reported by patients suffering from apathetic behaviour (Guercio et al., 2015).

Although the neurobiological basis of apathy is not fully elucidated yet, it has been suggested that the development and progression of apathetic behaviour occurs due to dysfunction in the basal ganglia (BG) and frontal regions of the brain (Malloy & Boyle, 2005). Namely, it has been reported that apathy is often seen in patients with lesions in the prefrontal regions of the brain and in specific structures of the BG (Stuss, Van Reekum, & Murphy, 2000)(Ishizaki & Mimura, 2011). The BG and their connections with the prefrontal cortex (PFC) are essential to decision-making and motivation (Balleine, Delgado, & Hikosaka, 2007). Because these functions are impaired in patients with apathy, it has been suggested

that the prefrontal cortex-basal ganglia axis, which is one of the functional systems involved in self-generated purposeful behaviour (Levy & Dubois, 2006), plays a major role in the development of apathy. However, several steps are necessary to accomplish goal-directed behaviour. First, it is necessary to process and compare external and internal signals in order to influence the intention to act. Then, the plan of actions needs to be elaborated, initiated and executed. The behavioral responses are regulated by a feedback control possibly initiating a following process of goal-directed behavior. Therefore, apathy can be due to disturbances at any of these steps and apathy severity depends on which specific mechanism is disrupted in the process of goal-directed behaviour (GDB) (Levy & Dubois, 2006).

Specific parts of the frontal lobes and the BG are probably involved in the development of three different subtypes of apathy that are related to the specific mechanisms that can be disturbed in the process of goal-directed behaviour. The emotional, cognitive and behavioural subtypes, first proposed by Stuss et al. (2000), were later on replaced by the emotional-affective, cognitive and auto-activation subtypes proposed by Levy and Dubois (2006). The first one, the emotional-affective mechanism, can be ascribed to deficits in the orbital-medial prefrontal cortex (PFC), the ventral striatum and the amygdala. This type refers to the inability to establish the linkage between emotional-affective signals and ongoing behaviour. Secondly, disruption of cognitive processing could be explained by disturbances in the lateral PFC and its input to the dorsal caudate nuclei. This goes along with difficulties in elaborating a plan of action necessary for the ongoing behaviour. The third subtype includes difficulties in the auto-activation process that are mostly associated with problems in the internal parts of the globus pallidus (GPi), paramedian thalamic nuclei and dorsal medial PFC (dmPFC). The auto-activation subtype could be characterized by an inability to self-activate thoughts or self-initiate actions and has been suggested to be the most severe form of apathy (Levy & Dubois, 2006).

It has been found that the presence of apathy increases the risk of developing MCI, thereby predicting the progression from normal cognitive functioning to MCI (Geda et al., 2014). In addition, it has also been found to predict the progression from MCI to AD and the global cognitive decline in cognitive normal elderly (Guercio et al., 2015). So, apathy can be a first sign of mental diseases. Even more important, it could be seen as a marker of disease progression, which indicates the clinical relevance of apathetic behaviour even in the early stages of cognitive decline.

Imaging

Several imaging studies have revealed that the cognitive and executive function deficits seen in AD and its earlier stages could be due to abnormalities in connectivity networks between brain areas (Damoiseaux, 2012). It has therefore been suggested that dementia is a consequence of an alteration in the functional connectivity (FC) patterns and that these abnormal patterns could be potential biomarkers for the diagnosis of AD and early MCI

(McKenna, Koo, & Killiany, 2015). Changes of the connectivity reflect alterations of intrinsic brain activity (Sorg et al., 2007), what makes the study of intrinsic brain activity crucial for understanding the physiology of functional brain disorders as AD and MCI.

One way to investigate brain connectivity networks is during rest, since brain activity is present even in the absence of an external task. Resting state functional MRI (fMRI), which is based on the measurement of spontaneous coherent fluctuations of the blood oxygen level-dependent (BOLD) signals during rest, has shown that brain activity is organized in multiple interregional functional networks, the so-called resting state networks (RSNs) (Ding et al., 2015). These RSNs might be useful in that they could be associated with functions of neural systems distributed across the brain that are possibly related to cognitive and affective symptoms that are seen in neuropsychiatric disorders.

Studies aimed at FC patterns have reported several RSNs consisting of tightly functionally connected brain regions. Three key networks are the default mode network (DMN), the central executive (CEN) or frontoparietal network and the salience network (SN) (Di & Biswal, 2015). The DMN is the most active network in the absence of a cognitive task. It is often shown to be active during the performance of internally focused tasks, such as autobiographical memory and self-referential processes, and when a person is at wakeful rest for example during day-dreaming (Joo, Lim, & Lee, 2016). The key regions that are associated with the DMN are the ventral medial PFC (vmPFC), posterior cingulate/retrosplenial cortex (PCC), inferior parietal lobule, dmPFC and hippocampal formation (Buckner, Andrews-Hanna, & Schacter, 2008) (Yuen et al., 2014). On the other hand, the CEN has key nodes in the dorsolateral PFC (dlPFC) and the lateral posterior parietal cortex (lPPC). The areas of the CEN are crucial for cognitively demanding tasks, such as working memory and judgement and decision-making in the context of goal-directed behaviour (Joo, Lim, & Lee, 2016). However, this network is also known to be activated in the absence of a task (Joo, Lim, & Lee, 2016). Additionally, the SN serves as a bottom-up processor of salient experiences, followed by the recruitment of other large-scale networks to influence ensuing behaviour in response to several internal and external stimuli. The SN primarily consists of the dorsal anterior cingulate cortex (ACC), ventrolateral PFC (vlPFC) and the anterior insula (AI) (Yuen et al., 2014)(Joo, Lim, & Lee, 2016). The right AI plays a crucial role in switching between activation of the CEN and DMN (Menon & Uddin, 2010). As reported by Sridharan et al. (2008), these two networks are known to interact in a competitive way during cognitive information processing. Moreover, as regulated by the SN, activity of both CEN and DMN fluctuates in a competitive way also during task-free resting state conditions (Sridharan, Levitin, & Menon, 2008).

Alterations in resting state functional connectivity patterns / RSFC

RSNs in aMCI patients

Altered RSNs have been reported in patients with aMCI, which indicates that FC is already deteriorated in the very first stages of AD pathology (Menon & Uddin, 2010). Several resting-

state studies report a decreased FC in the DMN (McKenna, Koo, & Killiany, 2015) (Hafkemeijer, van der Grond, & Rombouts, 2012), however, some studies found evidence for increased FC in this network (Bai et al., 2011)(Gardini et al., 2015)(Damoiseaux, 2012). In patients with mild AD, a decrease in FC between DMN associated areas is often reported, often followed by an even more extensive decreased FC between several areas in the DMN in moderate AD subjects (Hafkemeijer, van der Grond, & Rombouts, 2012). On the other hand, the most consistent finding in studies with aMCI patients is increased FC between posterior default mode brain regions compared with healthy controls (Bai et al., 2011)(Gardini et al., 2015)(Sorg et al., 2007). Recently, Gardini et al. (2015) indicated increased FC between the mPFC and PCC and between the PCC and mediotemporal regions in aMCI patients. Notably, a follow-up study of Bai et al. (2011) in patients with aMCI has shown that in time the connectivity patterns in posterior areas became less aberrant, whereas connectivity in frontal default mode regions was increased then. This was followed by a decrease in connectivity in frontal default mode areas (Bai, et al., 2011). Also, Sorg et al. (2007) have reported altered FC in posterior areas of the DMN in patients with aMCI, accompanied by reduced activity in the PCC and bilateral superior parietal lobes.

The shift in FC from increased connectivity in the early stages of MCI towards decreased connectivity patterns as disease progresses might be explained by a possible compensatory mechanism. This mechanism could be activated and triggered by functional loss of posterior brain areas, which leads to the recruitment of alternative networks to compensate for the loss of cognitive functions. Possibly, hyper-connectivity within parts of the DMN precedes the hypo-connectivity of these brain regions within the DMN, which may be the signal of neuronal loss in the early phase of neurodegeneration that is leading to brain dysfunction (Damoiseaux, 2012). This might also explain the decreased connectivity in posterior default mode areas and increased connectivity in frontal regions in mild AD patients that progresses into decreased connectivity throughout the entire DMN in moderate AD subjects (Damoiseaux, Prater, Miller, & Greicius, 2012).

Abnormalities in the SN and CEN appear to be less obvious in studies with aMCI patients. McKenna et al. (2015) found a small decrease in RSFC of the ACC, which is a key node of the SN areas. Additionally, Ho et al. (2014) reported decreased FC in the SN of these patients, especially between the AI, middle frontal gyri (MFGs) and left angular gyrus (AG). These authors also found differences in CEN connectivity, with diminished FC in associated CEN areas in aMCI patients (He et al., 2014)(Sorg et al., 2007). However, Wang and colleagues (2015) reported a slight increase in CEN FC in the MCI group, followed by a sharp decrease in connectivity in the AD subjects. This increase in FC, on the one hand, again might be explained by a coherent compensatory recruitment in MCI patients (Wang et al., 2015). On the other hand, the decrease in RSFC between the SN, CEN and DMN that is sometimes also reported, has been suggested to occur due to the normal aging process and might therefore be associated with the cognitive decline in elderly people as well as in patients with aMCI (He et al., 2014).

In conclusion, these different suggestions are based on very contradictory results on the connectivity patterns of the SN and CEN in patients with MCI. This emphasizes the need for further investigation.

RSNs and apathy

Apathy is related to executive dysfunction in the early phases of cognitive decline. Executive function is considered to rely upon a shared fronto-parietal network, which enables the integration and control of executive functions (Barbey et al., 2012). A lesion study suggested that affection of the fronto-parietal connections may lead to deficits in executive functioning, such as breakdown of complex goal-directed behaviour (Barbey, & al., 2012). This could be due to a disrupted transmission of the relevant signal to the frontal cortex, which in its turn becomes incapable to select, initiate, maintain and shift the programs of action (Levy & Dubois, 2006).

On the other hand, it has been suggested by Guimarães et al. (2008) that apathy in the early stages of dementia may be the result of a dysfunction of emotional-affective processing, one of the subtypes of apathy, which is related to the linkage of emotional-affective signals to on-going behaviour. The related processes take place in the vmPFC and connections with the ventral striatum, resulting in an impairment in striatal dopaminergic activation (Guimaraes et al., 2008). Dysfunction in this pathway of signal detection and decision-making for subsequent behaviour may contribute to the deficits seen in subjects with apathy, such as breakdown of goal-directed behaviour and lack of motivation (Guercio et al., 2015). In terms of RSNs, the SN is essential for the detection of salient signals. After detection, the SN will recruit other networks, such as the DMN and the CEN, to influence behaviour (Yuen et al., 2014)(Hyun Joo, Kook Lim, & Uk Lee, 2016). The DMN is especially active during internally focused activities (Buckner, Andrews-Hanna, & Schacter, 2008), whereas the CEN is very important in tasks as judgement and decision making in the context of goal-directed behaviour (Joo, Lim, & Lee, 2016). Linking these functions to the symptoms belonging to apathetic behaviour, it could be suggested that the connectivity between and within the SN and CEN is decreased, resulting in an increased activity of the DMN, since the DMN and CEN act in a sort of competitive way.

Also, as Guimarães et al. hypothesized, apathy in the early phases of dementia could be related to disturbed connections between the vmPFC and ventral striatum (Guimaraes et al., 2008). It has been shown that the medial orbito-frontal regions and medial portions of the PFC, which are both parts of the vmPFC, are involved in the human decision-making process (Rushworth et al., 2007). This process is often disrupted in patients with apathy (Guercio et al., 2015). Marshall et al. (2007) used PET in mild to moderate AD patients and found that apathy was related to hypometabolism in the vmPFC, including the medial orbito-frontal cortex (OFC). This suggests alterations in the connectivity patterns of the OFC, which is reported as part of the DMN (Buckner, Andrews-Hanna, & Schacter, 2008)(Yuen et al., 2014).

Moreover, another specific region related to the vmPFC that is frequently reported to show structural or metabolic abnormalities in subjects suffering from apathy is the ACC, an

important component of the SN (Guimaraes et al., 2008). This area has been considered to be crucial for motivation; it should play an important role in the initiation of cognitive and behavioural activities (Rushworth & Behrens, 2008). As expected following the motivational disturbances seen in apathy, a core role for the ACC in apathetic patients has been reported. Onoda and Yamaguchi have reported a decreased FC of the ACC with the mPFC, PCC, precuneus, amygdala and BG. Since the mPFC, PCC and precuneus constitute the DMN, whereas the amygdala and BG belong to the limbic circuitry, it has been suggested that the internal mental models of the DMN are based on information coming from limbic systems (Onoda & Yamaguchi, 2015). Taken together, this could suggest that the ACC in patients with apathy might be less efficient at integrating information from the internal mental models of the DMN as well as integrating emotional processing in the amygdala. This might result in a decreased FC within the CEN and between the SN and CEN, together with an increased FC within the DMN. Moreover, it could also be hypothesized that behaviour-related processing of the BG is not connected to incoming salience information processing of the ACC, resulting in a failure to transmit this information to the BG and a decreased FC within the BG.

Concluding, some of the few resting state studies that have been conducted in apathetic patients reported patterns of decreased RSFC within the SN, whereas others showed an unexpected increased FC of the right AI of the SN with the right dlPFC of the CEN (Yuen et al., 2014). Obviously, more research is needed in order to elucidate the suggested connectivity patterns of the RSNs in patients with apathy.

Objectives

Previous research has used resting-state fMRI to investigate RSFC and RSNs in both MCI and apathetic subjects. However, the relationship between RSFC in aMCI with apathy has not been evaluated before. In this study, resting state fMRI data will be analysed in order to elucidate the neural correlates of apathy in aMCI. This will enhance our understanding of the biological changes occurring due to the development of apathy in aMCI patients. We expect to find functional differences resulting from the development and severity of apathy in aMCI subjects compared to control subjects.

MCI patients mostly show decreased FC of the posterior DMN that is followed by decreased FC throughout the entire DMN. Furthermore, based on apathy research we expect to find increased FC of the DMN. Because apathy could be seen as an important marker of dementia progression (Guercio & al, 2015)(Geda, et al., 2014), this striking FC data emphasizes the need to explore the relationship between apathy and MCI in more detail.

More specifically, salience processing of the SN has been thought to attribute motivational value to a stimulus and promote approach toward or retreat from a stimulus (Yuen et al., 2014). Since this function seems to be impaired in patients with apathy (Guercio et al., 2015), we expect to find decreased salience integration in the ACC of these patients, along with a decreased RSFC within the SN. Furthermore, the SN in apathetic aMCI patients is probably less efficient at integrating incoming information from the internal models of the

DMN (Onoda & Yamaguchi, 2015), which could result in a less obvious activation and a decreased FC of the CEN, associated with an increased FC of the DMN. Moreover, apathy is related to a reduction in goal-directed behaviour, which could be the result of disrupted information processing within the CEN, but also between the PFC/ACC and BG. Therefore, we expect to find decreased RSFC within the CEN and the BG as well as a decrease in connectivity between the BG and the SN.

Methods

Participants

Patients between 60 and 80 years of age were recruited from several Memory Clinics in the North of the Netherlands. Moreover, patients and healthy controls were recruited via advertisements in local newspapers. These participants were evaluated on apathy and had to be diagnosed with aMCI by a clinician and neuropsychologist to participate. All subjects had to fill out a detailed questionnaire concerning safety aspects of the research in relation to the 3 Tesla magnetic field and the MRI environment. MR incompatible implants in the body, metal particles in the eyes and tattoos containing specific red pigments form a safety risk. Subjects facing any of these criteria were excluded. Also, subjects with claustrophobia were excluded. Furthermore, any subject diagnosed with AD by NINCDS/ADRDA criteria and DSM-IV criteria was excluded. Clinical evaluation together with the test results subdivided all subjects in 31 MCI patients and 20 healthy controls that were age, sex and education matched to the aMCI subjects. All participants gave written informed consent and the study was approved by the Medical Ethics Committee (METc) of the University Medical Center Groningen (UMCG). All procedures were carried out according to the Declaration of Helsinki.

Cognitive and behavioural assessment

In order to assess the general mental state of the individuals, the Mini Mental State Examination (MMSE) was conducted in each participant. This is a short examination of cognitive ability with a maximum score of 30. Scores of 28-30 are considered normal, 22-28 as cognitively impaired and scores below 22 as demented (Folstein, Folstein, & McHugh, 1975)(Petersen et al., 1999). Besides, the Rey Auditory Verbal Learning Test (RAVLT) was used to test memory. This neuropsychological test has been demonstrated to identify MCI subjects at risk for dementia (Lezak, Howieson, & Loring, 2004). Participants were given a list containing 15 unrelated words and were asked to repeat them. This test was administered in five trials using the same word list. MCI was defined as lower than 1.5 standard deviation of the mean of their own reference group. Furthermore, the Apathy Evaluation Scale clinician version (AES-C), developed to quantify and characterize apathy in adults aged 55 years and older, was conducted in all subjects (Marin, Biedrzycki, & Firinciogullari, 1991). This is a semi-structured interview consisting of 18 questions to the subject's thoughts, feelings and actions in the preceding four weeks. Scores range from 18 to 72 (Clarke et al., 2007)(Robert et al., 2009).

Neuropsychological assessment was also conducted. This included standardized tests for global function and cognitive assessment that were used to assess the cognitive status of all subjects. In general, most of these tests are sensitive in dementia patients, such as the DSST, and can identify MCI subjects at risk for dementia, such as the RAVLT (Lezak, Howieson, & Loring, 2004). Table 1 shows an overview of the neuropsychological tests and corresponding assessments.

Neuropsychological test	Assessment
Digit Symbol Substitution Test (DSST)	Memory in digit-symbol-coding performance
Digit Span - Digit Forward - Digit Backward	Mental processes - Attention - Working memory and reversing operations
Rey Auditory Verbal Learning Test (RAVLT)	Memory
Boston Naming Test (BNT)	Confrontational word retrieval
Trail Making Test (TMT) – A & B	Visual attention and task switching
Hayling Test	Executive function
Stroop Test	Executive function and inhibitory control
Amsterdams Korte Termijn Geheugen Test	Working memory

Table 1.
Neuropsychological assessment including standardized tests for global function and cognitive assessment.

Image acquisition

MRI data was/were acquired using a 3.0 Tesla whole body scanner (Philips Intera Achieva, Best, The Netherlands) equipped with a 32-channel SENSE head-coil for excitation and signal collection. This scanner is located at the Neuroimaging Center of the UMCG in Groningen. Foam padding and earplugs were used to limit head motion and reduce scanner noise. All 51 subjects underwent a resting-state fMRI, task-fMRI, DTI and MRS scanning during the same sessions.

For resting-state fMRI, data were acquired using a T2* weighted gradient echo-echo planar imaging (GE-EPI) sequence with a descending slice acquisition order and the following parameters: TR = 2000 ms; TE = 30 ms; FA = 70 degrees; matrix size = 64 voxels x 64 voxels; voxel size = 3,4375 mm x 3,4375 mm; field of view (FOV) = 220 mm x 220 mm x 121,8 mm; slice thickness = 3 mm; slice gap = 0 mm; axial slices = 37; functional volumes = 300; scan duration = 608 seconds. The images were acquired parallel to the anterior-posterior commissure plane. During the fMRI resting-state scan, all subjects were instructed to keep their eyes closed, to stay as motionless as possible, to think of nothing in particular and to not fall asleep.

fMRI data analyses

Preprocessing

MRI-images were converted from PAR/REC to NIFTI by using an in-house built script in Matlab. Functional MRI data were preprocessed by using the statistical parametric mapping (SPM12b; FIL Wellcome Department of Imaging Neuroscience, London, UK) running in Matlab 2013a. Images were first reoriented to the anterior commissure – posterior commissure plane. After that, images were slice-time corrected. Images were then realigned to the mean image. Each subject's movement parameters were examined and datasets with more than sudden 3 mm maximum translation in x, y or z direction, or 3 degrees of

maximum rotation about three axes were excluded (n=4). After realignment, the functional images were co-registered to the T1-weighted image. The T1-image was normalized to the standard T1-MNI (Montreal Neurological Image) brain (with a voxel size 3 3 3 mm to reduce memory load in the ICA) of SPM and the same transformation was applied to the functional images. The functional images were then spatially smoothed with a Gaussian kernel of 8 mm FWHM.

Independent Component Analysis (ICA)

We performed the ICA twice. First we used data of all subjects, including controls, to compare both groups. Because we also wanted to correlate AES scores of MCI subjects to connectivity patterns, we selected data of MCI subjects only the second time. This will lead to a more specific ICA, which is preferred for the analyses.

Group ICA for fMRI toolbox (GIFT version 3.0) established for the analysis of fMRI data was used to run the ICA. The toolbox supports a group ICA approach. First, GIFT concatenates the individual data across time (I data reduction). Then the data is decomposed in independent components (II application of the ICA algorithm). This is followed by the computation of the subject specific components and time courses (III back-reconstruction).

In step (I), data from each subject were reduced by using PCA. Hereby computational complexity was reduced while most of the information content of the data was preserved. After concatenating the resulting volumes, the number of independent components was estimated by the GIFT dimensionality estimation tool based on the aggregated data. This resulted in 42 estimated independent components based on the data of all subjects and 44 estimated independent components for the MCI subjects only. The final reduction step according to these estimated number of components was achieved by PCA again, thereby using the original preprocessed fMRI data.

For step (II) we chose the Infomax algorithm and a GM mask based on all subjects. Also, we selected ICASSO to determine the reliability of ICA algorithm. This procedure runs the ICA algorithm several times to determine the algorithmic reliability or stability. We selected for the RandInit mode and 20 times of serial ICA run, with a minimum of 16 and a maximum of 20. In SetupDefaults we chose intensity normalization for data pre-processing, no scaling of the results and spatial-temporal regression as back-reconstruction type. Default settings were chosen for the other options.

In the final stage of back-reconstruction (III), time courses and spatial maps were computed for each subject by spatial temporal regression. After back-reconstruction, the mean spatial maps of each group were transformed to Z-scores for display.

Postprocessing

Selection of the components of interest for both healthy controls and patients was done by selecting the components that showed a large spatial overlap with *a priori* defined

anatomical masks. We used the WFU PickAtlas Tool (Wake Forest University, Version 2.1) to generate these anatomical masks based on the Talairach Daemon (TD) database as well as on other human atlases (Maldjian et al., 2003) (Maldjian, Laurienti, & Burdette, 2004). We generated masks for four RSNs based on previous research; DMN (posterior cingulate, inferior parietal lobule, precuneus, angular gyrus, medial PFC), CEN (superior frontal gyrus/dorsolateral PFC, posterior parietal cortex/inferior and superior parietal lobule), SN (anterior cingulate, insula, inferior frontal gyrus/ventrolateral PFC) and BG (lentiform nucleus, left and right thalamus, left and right amygdala, left and right supplementary motor area, left and right Heschl/transverse temporal gyrus).

Display GUI was used to sort and visualize components after ICA analysis. We selected Component Explorer to sort all components, with correlation for sorting criteria and the spatial sorting function. By selecting the generated ROI masks in this sorting step, the components that correspond best with the specific mask are sorted high. We selected the IC patterns located in the cortex that represented functionally relevant RSNs that were previously described. The remaining IC patterns were not of our interest and/or attributed to forms of artefacts, such as tissue border artefacts near the ventricular system, the skull and cerebrospinal fluid space.

Group comparisons

Group differences for within-network functional connectivity were investigated using a two-sample t-test random effect design in SPM. The analyses were performed based on the individual subjects maps of the selected components. This analysis shows brain areas that are differently connected to the rest of the RSN components in MCI patients compared to HC. Results were regarded significant at a threshold of $P < .05$ family wise error (FWE) corrected on cluster level for the whole brain, with an initial threshold of $P < 0.001$ uncorrected.

For within-network functional connectivity in the MCI group only, the relationship with apathy was analyzed in SPM using a multiple regression design with AES scores as covariates (cluster-level $pFWE < 0.05$, with initial threshold of $p < .001$ uncorrected).

To investigate group differences in between-network functional connectivity, we used the Functional Connectivity Toolbox (FNC, version 2,3a, MIALAB Software). We added a two-way contrast. For time course (TC) filter we selected: $0.05 < 0.95 < 1$ and for units 'normalization'. Lag-shift of 3 seconds were applied. TR was 2 seconds. We selected 'Mean S All' and ran the Lag-Shift algorithm. Both positive and negative correlations were taken into account. The threshold was set at $p < 0.05$.

Statistical analyses for correlation between AES score and between-network functional connectivity in the MCI group were performed using Spearman's correlation in Statistical Package for the Social Sciences (SPSS, version 22). Analyses were based on the correlation matrix of components that was extracted from the FNC toolbox.

Results

Initially, 31 MCI patients and twenty healthy controls were included. However, due to excessive head motion during the resting state, we had to exclude four subjects. This made us end up with data of 29 MCI patients and eighteen healthy controls (table 2). The distribution of the AES scores is displayed in figure 1.

	MCI patients	**Healthy controls**
N	29	18
Mean age	68 ± 5.1	67,4 ± 4,7
Mean MMSE score	28,4 ± 1,7	28,9 ± 1,1
Mean AES score	31,3 ± 10,4	26,3 ± 4,7

Table 2.

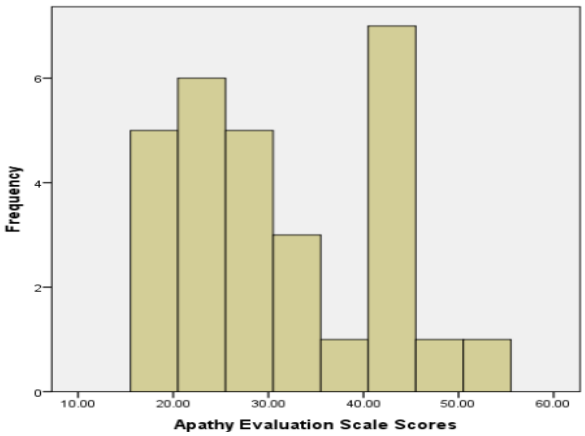

Figure 1.
Distribution of AES scores in aMCI patients.

Based on the data of all included subjects, the ICA resulted in 42 independent components. We selected eight components, which represented the RSNs of interest. Based on visual selection after component sorting, we classified component 22 as the posterior DMN and component 32 as the anterior DMN. Component 16 was classified as the left CEN and component 17 completes the CEN as the right part. We regarded components 13, 15 and 41 as comprising the SN. The BGN was displayed in component 10. These components are depicted in figure 2.

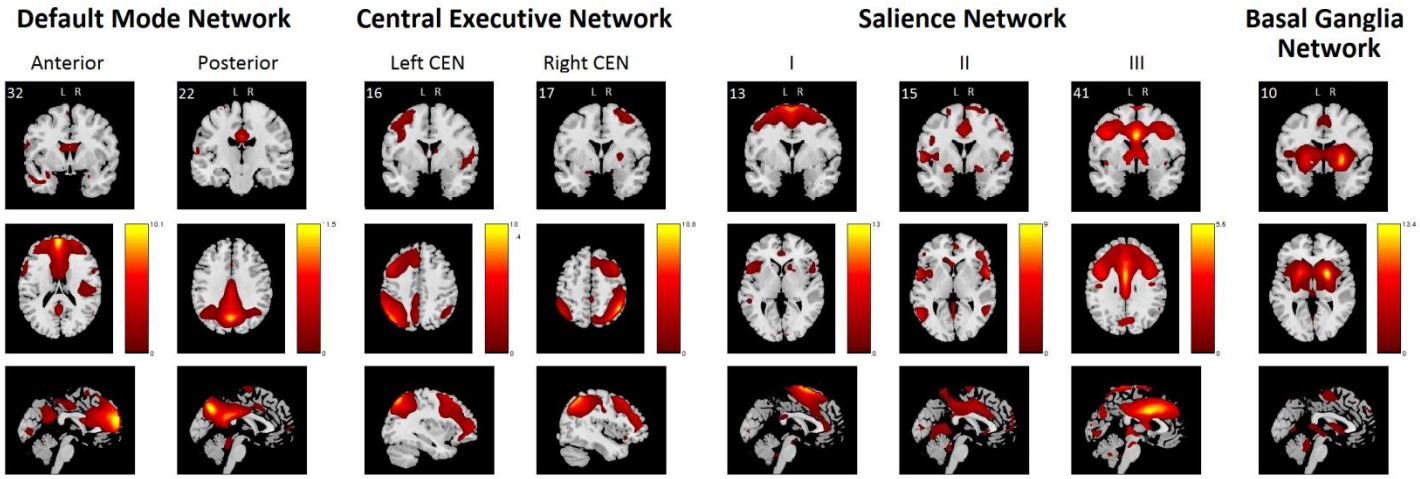

Figure 2.
Spatial maps of the selected independent components based on the data of all subjects. The axial brain sections are displayed in neurological convention.

Based on the data of MCI subjects only, the ICA resulted in 44 independent components. From these, we selected nine components, which represented the RSNs of interest. Again, we sorted these components and upon visual selection component 16 was classified as the anterior DMN and component 4 as the posterior part of the DMN. Components 25 (left) and 30 (right) were found to form the CEN. For the SN, we selected four components. These were component 13 (cingulate gyrus), 31 (anterior cingulate gyrus), 32 (insula) and 40 (amygdala). The BGN was displayed in component 18. These components are shown in figure 3.

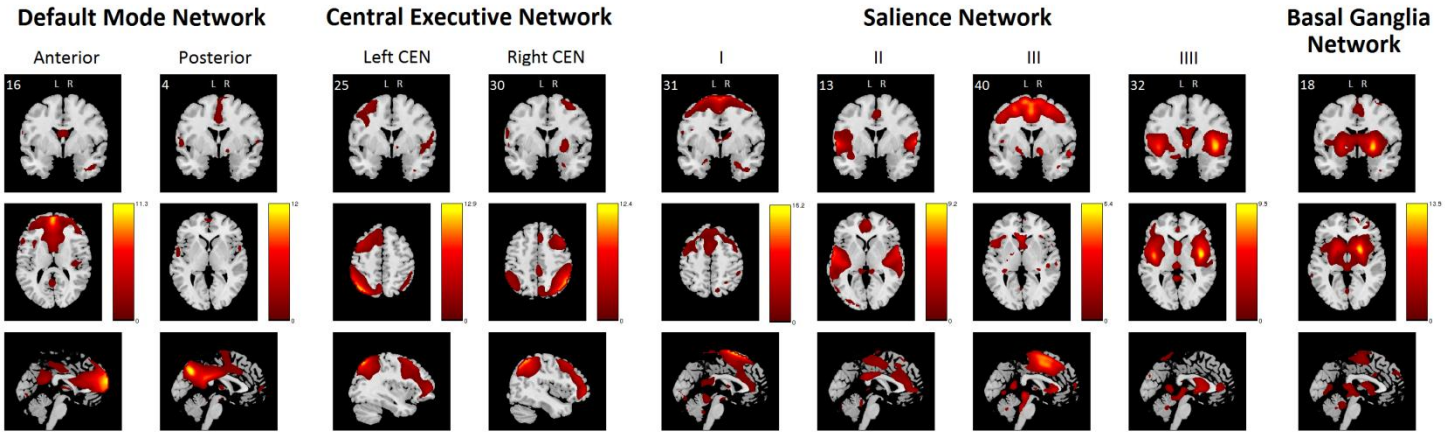

Figure 3.
Spatial maps of the selected independent components based on the data of MCI subjects. The axial brain sections are displayed in neurological convention.

Within-network connectivity

MCI patients versus healthy controls

Significant differences in within-network functional connectivity were found between the total group of MCI patients and healthy controls (HCs). Significant stronger connectivity was found in the cuneus of component 17 of the CEN in the MCI group compared to HCs (P_{FWE} = .044, T = 4.49, peak MNI-coordinates -9 -88 29, Z = 4.06)(fig. 4a). We also found stronger connectivity in the MCI group in putamen (P_{FWE} = .211, T = 4.77, peak MNI-coordinates 30 -1 -4, Z = 4.27)(fig. 4b), medial frontal gyrus (P_{FWE} = .302, T = 4.56, peak MNI-coordinates -12 14 50, Z = 4.11))(fig. 4c) and thalamus (P_{FWE} = .330, T = 4.15, peak MNI-coordinates -27 -22 2, Z = 3.8)(fig. 4d) of component 17 compared with the HCs. However, these differences were not significant after pFWE-correction. Furthermore, after pFWE-correction we found significant stronger connectivity in the posterior cingulate cortex of component 41 (SN) in the MCI patients compared with the HCs (P_{FWE} = .034, T = 4.71, peak MNI-coordinates -24 -28 38, Z = 4.22)(fig. 4e).

In addition, we found weaker connectivity of the posterior cingulate cortex of component 15 (SN) in the MCI subjects compared with the HCs, although this was not significant after pFWE-correction (P_{FWE} =.333, T = 4.13, peak MNI-coordinates -12 -40 35, Z = 3.78)(fig. 4f).

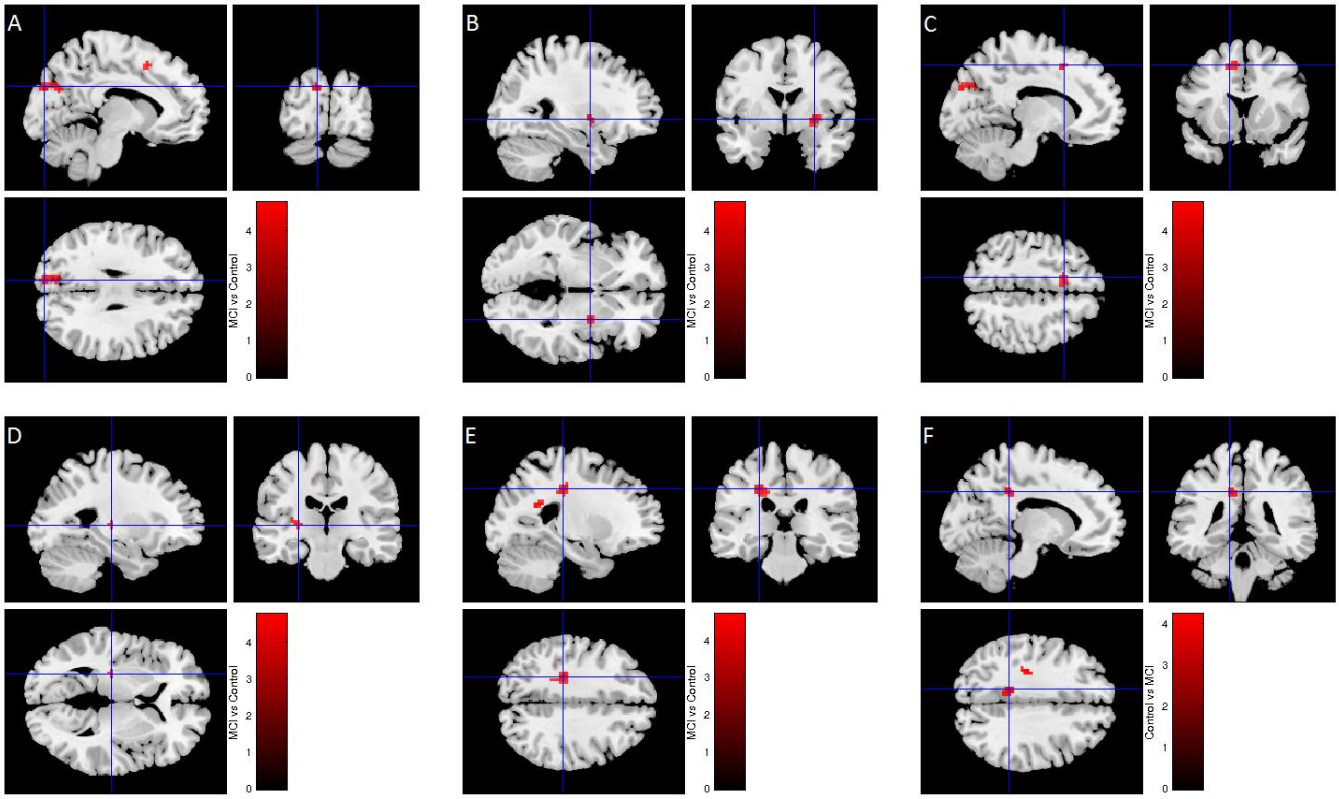

Figure 4.

Within-network functional connectivity between the total group of MCI patients and HCs. Stronger connectivity in (**A**) cuneus, (**B**) putamen, (**C**) medial frontal gyrus and (**D**) thalamus of component 17 (CEN) of MCI patients compared with HCs. B. (**E**) Stronger connectivity in posterior cingulate cortex of component 41 (SN) of MCI patients compared with HCs. (**F**) Weaker connectivity in posterior cingulate cortex of component 15 (SN) in MCI subjects compared with HCs.

Apathy in MCI patients

In the MCI patient group, higher AES scores were related to stronger connectivity in inferior parietal lobule of component 18 (BGN)(P_{FWE} = .08, T = 4.70, peak MNI-coordinates 39 -52 35, Z = 3.98)(fig. 5a), medial frontal gyrus in component 13 (SN)(P_{FWE} = .246, T = 4.93, peak MNI-coordinates -12 -22 59, Z = 4.13)(fig. 5b) and the middle cingulate cortex in component 31 (SN)(P_{FWE} = .273, T = 4.91, peak MNI-coordinates -6 5 35, Z = 4.11)(fig. 5c). Furthermore, stronger connectivity related to lower AES scores were found in caudate nucleus of component 18 (BGN)(P_{FWE} = .066, T = 5.29, peak MNI-coordinates -9 17 14, Z = 4.34)(fig. 6a), postcentral gyrus in component 25 of the CEN (P_{FWE} = .340, T = 4.39, peak MNI-coordinates -42 -28 38, Z = 3.78)(fig. 6b) and the precuneus (P_{FWE} = .191, T = 5.30, peak MNI-coordinates 33 -79 35, Z = 4.35)(fig. 6c) and superior parietal lobule (P_{FWE} = .317, T = 4.33, peak MNI-coordinates -15 -49 53, Z = 3.74) of component 4 (DMN)(fig. 6d). However, these results were not significant after pFWE-correction.

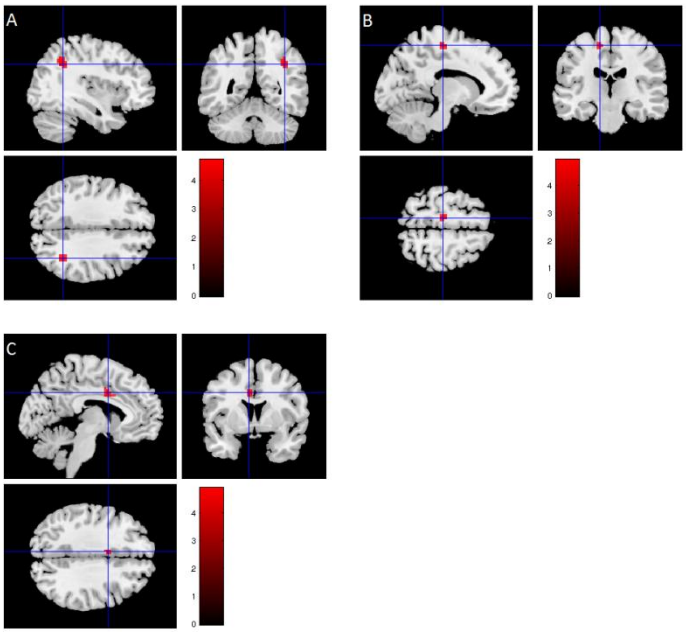

Figure 5.
Positive correlation between AES scores in MCI patients and within-network functional connectivity in (**A**) inferior parietal lobule of the BGN, (**B**) medial frontal gyrus in the SN and (**C**) middle cingulate cortex of the SN.

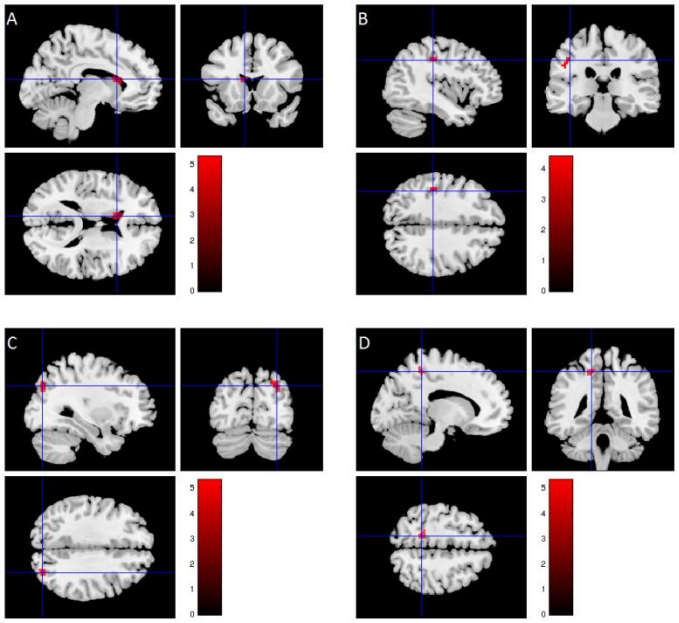

Figure 6.
Negative correlation between AES scores in MCI patients and within-network functional connectivity in (**A**) caudate nucleus in the BGN, (**B**) postcentral gyrus in the CEN and (**C**) precuneus and (**D**) superior parietal lobe of the SN.

Between-network connectivity

MCI patients versus healthy controls

Regarding between-network interactions, we found weaker connectivity from component 41 of the SN to component 32 of the DMN (posterior) in MCI subjects compared to the HC group ($P < .05$). Furthermore, weaker connectivity from component 32 of the DMN (posterior) to component 13 of the SN was found in MCI subjects compared to HCs ($P < .05$). However, after FDR-correction no significant differences in between-network connectivity were found between the MCI subjects and HCs.

Apathy in MCI patients

Within the MCI patient group, we found a negative correlation between AES scores and the connection between component 13 (SN) and component 16 of the DMN (anterior)($C = -.382$, $P = .041$). Furthermore, a positive correlation was found between AES scores and component 32 (SN) and component 40 of the SN ($C = .496$, $P = .006$).

Discussion

In this study, resting state fMRI was used to assess functional connectivity related to apathy in subjects with MCI. Differences in central-executive network (CEN), salience network (SN) and default mode network (DMN) connectivity and interactions were found between MCI subjects and healthy control subjects. Furthermore, functional connectivity patterns within the four networks and between SN and DMN were shown to be related to apathy in patients with MCI.

Regarding within-network functional connectivity in aMCI subjects compared with HCs, we found increased connectivity patterns in the cuneus, putamen, medial prefrontal gyrus and thalamus of the CEN. This is in contrast to other findings regarding resting state connectivity in aMCI patients that mostly report decreased FC of these regions in the CEN (Lau, Leung, Lee, & Law, 2016). However, similar to our results, Wang and colleagues (2015) found a slight increase in CEN FC in aMCI subjects compared with HCs. On the other hand, Wang et al. (2015) reported a sharp decrease in connectivity in the CEN in AD subjects in a follow-up study. The increase in CEN FC in aMCI in the study of Wang et al. could be interpreted as a coherent compensatory mechanism for the recruitment of cognitive resources in the aMCI patients (Li, et al., 2014)(Wang et al., 2015). The decrease in FC in the CEN in AD subjects thereafter (Wang et al., 2015) points at the inability of the specific regions to compensate for the severity of cognitive impairment in these AD patients. According to this coherent compensatory mechanism, our results could be related to the possible compensation for cognitive loss that is associated with these areas in aMCI patients.

Furthermore, there is a lot of discrepancy concerning connectivity in the medial prefrontal cortex (MPFC) in general in aMCI. Decreases in resting state connectivity of the MPFC where observed in aMCI (Li et al., 2015), although others did not observe any hypoactivity in these regions in aMCI subjects (Lau, Leung, Lee, & Law, 2016). A possible explanation could be that the hypoactivity of these prefrontal brain areas is not a defining feature of aMCI (Lau, Leung, Lee, & Law, 2016). Disturbances in connectivity in specific regions within the CEN in aMCI could be associated with impairments in working memory that are seen in these patients (Joo, Lim, & Lee, 2016). Anterior prefrontal brain areas, for example, have been associated with phonological memory storage and are considered the neural substrates of working memory (Müller & Knight, 2006). On the other hand, the CEN has also been associated with judgement and decision-making in the context of goal-directed behaviour (Joo, Lim, & Lee, 2016). Focal lesions of the medial-dorsal thalamic nuclei and other parts of the BG are thought to be associated with diminished voluntary goal-directed behaviour, which is also referred to as apathy (Levy & Dubois, 2006). So, apathy could be one of the clinical consequences of disturbances in specific parts of the CEN that are associated with generation and control of self-generated purposeful behaviour (Levy & Dubois, 2006).

Furthermore, in aMCI subjects compared with HC, we found increased connectivity in the posterior / middle cingulate cortex (PCC / MCC) in the SN, whereas decreased connectivity in the PCC in the SN was also found. Previous studies also reported different results on functional connectivity in SN in aMCI subjects. He et al. (2014) found structural and functional impairments in organization of the SN in aMCI and AD patients. In addition, Minoshima et al. (1997) reported metabolic reduction in the PCC in early AD. In more detail, disturbances within the PCC are often associated with cognitive impairments that are seen in aMCI patients, including memory function and attention (Leech & Sharp, 2014). Besides, connectivity within the SN has been associated with guiding behaviour in response to internal and external stimuli (Joo, Lim, & Lee, 2016). Thus, disturbances in the PCC and other parts of the cingulate cortex in the SN in aMCI could be linked to difficulties in focussing attention on incoming stimuli and impairments in memory, both typical for aMCI patients.

Based on previous studies, the DMN is most often the first network affected in dementia patients. In our study, the connectivity in aMCI compared with HCs was investigated. Remarkably, we did not find any alterations regarding within-DMN FC in aMCI subjects compared with HCs. Possibly, the presence of apathy has a strong influence on brain connectivity in aMCI subjects. This suggestion is strengthened by the disturbances in CEN connectivity that are found in this study. The disturbances in CEN indicate impairments in goal-directed behaviour that are specifically associated with apathy.

Interesting results were found with respect to correlations between within-network functional connectivity and apathy. A positive correlation was found between apathy in aMCI subjects and FC in the inferior parietal lobule (IPL) of the basal ganglia network (BGN). It has been found that conscious intention emerges before action or movement onset as a result of increased activity within the IPL (Desmurget & Sirigu, 2012). Moreover, abnormality in the IPL was regarded as a sensitive marker for the transition from MCI to early stages of AD, which emphasizes the possible role of apathy in the progression from MCI to AD (Zhang, et al., 2012). Namely, disturbances in the connection between IPL and BG could lead to difficulties with intentional movements and executive dysfunction, that is also seen in apathy in the early phases of cognitive impairment (Barbey et al., 2012).

There was a positive correlation between apathy in aMCI and FC in the MPFC and MCC of the SN. Remarkably, previous studies reported an association between apathy and atrophy of the MPFC and also parts of the cingulate cortex in dementia patients (Rosen et al., 2005)(Massimo, et al., 2009). Matsuoka et al. (2015) found that atrophy in the PCC was correlated with apathy in patients (Matsuoka et al., 2015). The positive correlation between apathy and MPFC and MCC connectivity in aMCI might be a reaction to compensate for possible atrophy in both areas. Connectivity in the cingulate cortex could be associated with functions of the CEN in decision making, goal-directed behaviour and motivation (Joo, Lim, & Lee, 2016). Disturbances in FC in MCC would explain the impairments in these executive functions related to the CEN that are seen in apathy patients. Moreover, the three different types of apathy that are characterized by different symptoms might also be distinguished by

differences in brain connectivity (Levy & Dubois, 2006). Specifically, the emotional-affective subtype may be related to lesions or impairments in the MPFC. Alterations in connectivity in the MPFC have been associated with the inability to establish the link between emotional-affective signals and the on-going behaviour, as is seen in apathy (Levy & Dubois, 2006).

A negative correlation between apathy in aMCI patients and FC in the caudate body of the BGN was found. In general, several basal ganglia – thalamocortical loops have been identified. One of these loops comprises cortical projections to the caudate nucleus (Parent & Hazrati, 1995). The neural circuits that link the basal ganglia with the cerebral cortex, such as the cingulate circuit, are involved in the generation and control of voluntary movement (Hoover & Strick, 1993). The decreased FC related to apathy in aMCI patients in the caudate body that is connected to the BGN might explain the impairments in these specific functions in apathy.

We found a negative correlation between apathy in aMCI patients with the part of postcentral gyrus (PCG), the location of the somatosensory cortex, that is associated with the CEN. Activity preceding a motor act as well as sensory information processing is controlled by the somatosensory cortex (Ford, Roach, Faustman, & Mathalon, 2008). Disturbances in this area and desynchronization of the sensory and motor systems could lead to difficulties in decision making and motivational behaviour (Ford, Roach, Faustman, & Mathalon, 2008). Therefore, the disturbances in connectivity in the postcentral gyrus that were found in association with the CEN could be linked to problems with intentional actions that are also seen in patients with apathy (Levy & Dubois, 2006).

A negative correlation between apathy in aMCI patients and FC in the precuneus and superior parietal lobe (SPL) of the DMN was found. A decreased FC of the precuneus with the SN was reported by Onoda and Yamaguchi (2015). They suggested that the SN in patients with apathy could be less effective at integrating information from the internal mental models of the DMN (Onoda & Yamaguchi, 2015). Besides, the SPL has been associated with imagination and execution of movement (Gerardin et al., 2000). Thus, in patients with apathy disturbances in connection between the SPL and other networks might be associated with impairments in goal-directed and intentional movements.

Regarding between-network FC, we found decreased connectivity between the SN and the posterior DMN in aMCI compared with HCs. Besides, we found a decreased FC between the posterior DMN and the SN in aMCI subjects compared with HCs. It has been shown that FC of both SN and DMN is altered in aMCI patients (McKenna, Koo, & Killiany, 2015)(Gardini et al., 2015)(Sorg, Riedl, Mühlau, & al., 2007). Disturbed connections between the SN and the posterior part of the DMN could lead to difficulties with the integration of signals coming from the posterior DMN, such as autobiographical memory, default mode (rest) and theory of mind (Spreng, Mar, & A., 2009). These functions might be impaired in patients suffering aMCI, but alterations in default mode and theory of mind are also seen in apathy (Petersen et al., 1999)(Levy & Dubois, 2006).

Besides, we found a negative correlation between apathy and FC between the SN and the anterior DMN in aMCI. On the other hand, we found a positive correlation between apathy and FC between different components of the SN in aMCI. A possible explanation for this could be that stronger connectivity within the SN might lead to aberrant connections with other regions in the DMN or CEN. As mentioned, Onoda and Yamaguchi (2015) also reported a decreased FC of the key node of the SN, the ACC, with regions that constitute the DMN. According to them, the SN is less effective at integrating incoming information from the internal models of the DMN in apathy (Onoda & Yamaguchi, 2015). Probably, patients with apathy do not effectively integrate the incoming information leading to difficulties in goal-selection, planning and the initiation and execution phase of an action (Levy & Dubois, 2006).

Some limitations need to be addressed in data collection and analysis. Abnormalities in DMN, SN and CEN are frequently seen in psychiatry and neurological disorders. However, there are both consistencies and discrepancies among HCs, aMCI patients and AD patients. Amnestic MCI patients are characterized by memory complaints and possible impairments in other cognitive domains, which makes it hard to acquire complete homogeneous experimental groups. So, cognitive functions depend on activity of the corresponding brain regions, which could have influenced the results on brain connectivity in this study. At last, factors such as disease duration might influence functional connectivity patterns.

Regarding between-network connectivity in aMCI patients compared with HCs, we selected a lag-shift of 3 seconds using FNC toolbox, whereas for practical reasons, we used correlation values without lag-shift for between-network connectivity in aMCI patients correlated to AES scores. Therefore, between-network connectivity related to AES scores in aMCI patients has to be considered as connectivity between two areas at exactly the same moment. On the other hand, using a lag-shift of 3 seconds allowed us to find correlated connectivity patterns in a time frame of maximal 3 seconds. These different approaches make it difficult to compare results. However, differences in between-network connectivity of the group comparison were also significant without lag-shift. Therefore, our results on between-network connectivity can be compared.

This fMRI study demonstrated an association between apathy and FC in aMCI patients. Alterations in connectivity in aMCI compared with HCs were found in the CEN, SN and between components of the SN and DMN. The CEN has been associated with working memory and decision-making in the content of complex goal-directed behaviour, whereas the SN needs to activate the CEN upon evaluation of incoming signals from the DMN (Levy & Dubois, 2006). Therefore, disturbances in connectivity in any of these networks could be associated with cognitive impairments seen in aMCI, but also with impairments in apathy. This suggests that apathy is associated with alterations in brain connectivity seen in patients that suffer from aMCI and apathy. Moreover, FC in aMCI patients correlated with severity of apathy turned out to be disturbed in regions in CEN, SN, DMN and BGN. These regions were

mostly related to intentional movements, linking emotional information to on-going behaviour and executive function. Disturbances in these specific areas might be associated with various dysfunctional processes in the context of goal-directed behaviour (Levy & Dubois, 2006).

These results could be useful for understanding neural mechanisms underlying apathy and the role of apathy in the progression of MCI. Probably, abnormal brain connectivity patterns could be used as biomarkers for the diagnosis of early MCI (McKenna, Koo, & Killiany, 2015). However, more research is needed to elucidate the role of apathy in aMCI in more detail.

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