Chapter 7

Summary, general conclusions and discussion

Late life depression with psychotic symptoms is a severe life threatening condition. Patients suffering from this disease are often admitted to the clinical facilities of old age psychiatry and treated with ECT, according to the Dutch guideline (multidisciplinaire depressie richtlijn, addendum Ouderen Trimbos instituut, 2008). Studies evaluating ECT response showed significantly higher and faster response rates in patients with psychotic symptoms compared with patients without psychotic symptoms (Tew et al., 1999; Birkenhager et al., 2003; Petrides et al., 2001; Spaans et al, 2015). However, these findings were not supported in a recent meta-analysis (Haq et al., 2015). Conflicting results may have been caused by selection bias of the included studies in the meta-analysis and small and/or heterogenous patient samples. Studies evaluating ECT response in relation to well-defined symptom profiles of late life depression, including brain characteristics, may provide more consistent findings and contribute to response predicton of ECT in the future.

The primary objective of the present thesis was to evaluate the association between symptom profiles, especially psychotic symptoms, brain characteristics, ECT response and cognitive impairment in late life depression after short and long term follow-up.

Multiple imaging analysis techniques were used to measure structural abnormalities. Visual rating scales on MRI were applied to study pre-treatment grey and white matter abnormalities in relation to ECT response (**second chapter**), in relation to transient cognitive impairment during the course of ECT (**third chapter**), and in relation to cognitive impairment and survival after seven to 12 year follow-up (**sixth chapter**). Using voxel-based morphometry (VBM) we assessed regional grey matter volumes in relation to symptom profiles and ECT response in late life depression (**fourth chapter**). In addition to these structural MRI analyses, functional MRI resting state networks were analyzed using independent component analyses (ICA) comparing patients with depression with and without psychotic symptoms **(fifth chapter**). The current chapter summarizes the main results, discusses the methodological issues, and integrates the main findings of this thesis with those from earlier research focussing on late life depression with psychotic symptoms in relation to ECT response. In addition, this chapter also discusses future directions and clinical implications of the main findings.

Summary of main findings

In the **second chapter** of this thesis, structural brain abnormalities were evaluated in association with ECT response in patients with late life depression. Based on previous studies and the "subcortical ischemic depression" hypothesis we put forth the premise that medial temporal lobe atrophy (MTA), white matter hyperintensities (WMH) and global cortical atrophy (GCA) negatively affect the short-term response to ECT. A total of 81 patients were included in this study. Visual rating scales assessed MTA on the MRI coronal three-dimensional T1 images while WMH and GCA were assessed on the MRI FLAIR images before the start of ECT. Overall results showed that 74.1% of the patients responded to ECT and 48.1% of patients showed remission after ECT. A significant association was observed between moderate or severe MTA and a lower ECT response: patients without MTA had a three times greater chance to reach remission compared with patients with moderate or severe MTA. Remarkably, the presence or absence of MTA had no effect on the response rates of ECT in patients with psychotic symptoms. It should be noted, however, that patients with psychotic symptoms and severe MTA received an average of 17.2 ECT sessions compared with an average of 12.4 sessions for patients with psychotic symptoms without severe MTA. In disagreement with our hypothesis, an association between WMH or GCA and ECT response could not be observed.

We hypothesize that the neurotrophic effect of ECT is mediated through the medial temporal lobe and that patients with severe atrophy of this brain structure may have an impaired neurotrophic effect during ECT. In the future, it is important to evaluate long-term outcome after ECT and whether it is possible to predict the short and long-term risk of cognitive impairment based on pre-treatment MTA, WMH, and GCA (chapter 6).

Frail patients with late life depression may suffer from cognitive impairment during an ECT course, a transient confusional state. This transient cognitive impairment resolves when patients recover from their depression. Little is known about risk factors influencing confusional states during ECT. The **third chapter** of this thesis describes our study on this clinically relevant topic evaluating pre-ECT MTA, WMH and GCA in association with transient cognitive impairment during ECT. After stratifying for ECT modality, i.e. unilateral, bilateral, or switching from unilateral to bilateral, the results showed a significant negative association between moderate or severe WMH and MMSE scores during ECT in patients who switched from unilateral to bilateral treatment. After continuation with ECT, this association disappeared and MMSE scores improved. After the last ECT session, MMSE scores did not differ significantly between patients with and without moderate or severe WMH stratified for all ECT modalities. Significant associations were not observed between MTA or GCA and MMSE scores during or after ECT treatment.

These findings are in line with a previous study that showed that patients with widespread vascular damage to the brain experience profound confusional states, defined as delirium, more commonly than patients with cortical brain disorders (Hatano et al., 2013). In addition, other studies showed an increased risk of cognitive impairment in patients treated with bilateral ECT compared with patients who are treated with unilateral ECT only (O'Connor et al., 2010).

In the **fourth chapter** of this thesis, regional grey matter volumes and symptom profiles of late life depression in relation to ECT response were evaluated. VBM was used to determine regional differences of grey matter (GM) volume between subgroups of in total 55 patients and 23 matched healthy controls. Patients with late onset depression (age of onset of first episode after 55 years) and patients with early onset depression (age of onset of first episode before 55 years) showed similar remission rates. However, patients with late onset depression did show smaller regional GM volume of the bilateral lateral temporal cortex and in the total patient group smaller pre-treatment regional GM volume of the right lateral temporal cortex was associated with a better response. Larger pre-treatment volume of the premortor cortex was related to a faster speed of response to ECT. A possible explanation for this finding may be that agitated depression with increased motor activity is related to high ECT response rates (Hickie et al., 1996).

Late life depressed patients with psychotic symptoms showed significantly higher remission rates in response to ECT compared with patients without psychotic symptoms (70.8% vs 38.7%, respectively). Depressed patients with psychotic symptoms showed smaller regional GM volume of the left inferior frontal gyrus (IFG). A faster speed of response in all patients was related to smaller pre-treatment regional GM volume of the right IFG.

Due to the involvement of the IFG in response inhibition (Forstmann et al., 2008; Matthews et al., 2009; Wang et al., 2008) and appraisal of emotional information (Rahko et al., 2010; Liebermann et al., 2004) it is possible that the IFG is involved in the neural circuit that is excited during ECT. An explanation of our results is speculative. Activation of a pre-treatment dysfunctional IFG may add to a fast response, especially in the patients with psychotic symptoms who showed abnormalities in this brain region before treatment.

In the **fifth chapter** of this thesis, pre-ECT resting state functional connectivity (FC) was evaluated in depressed patients with psychotic symptoms and compared with depressed patients without psychotic symptoms. A total of 23 patients at site one (Amsterdam) and 26 patients at site two (Leuven) were included and rsfMRI recordings were obtained before ECT. Independent component analysis was used to compare resting state networks in patients with and without psychotic symptoms.

Results showed significantly decreased connectivity of the right part of the bilateral frontoparietal network in psychotic depressed patients compared with patients without psychotic symptoms in the sample of site one, but not in the sample of site two. This disparity may be due to a statistical power problem, possibly because at site two a longer duration of scanning time lead to a higher exclusion of psychotic patients with severe agitation.

A relation between pre-ECT resting state networks and depression severity was not observed at any of the two sites. These findings suggest that FC of the frontoparietal network is dependent on subtype of depression, i.e. presence of psychotic symptoms, rather than on severity of depression.

The results obtained with the sample of site one are in line with a study of Hyett and colleagues (2015), showing hypoconnectivity of the right frontoparietal network in patients with versus without melancholic symptoms. Is has been suggested that melancholic depression and depression with psychotic symptoms are two subtypes of depression that have a shared disease mechanism, since these subtypes of depression have similar identifiable defining features, i.e. severe weight loss or loss of appetite, psychomotor agitation or retardation, early morning awakening, excessive guilt, and worse mood in the morning (Caldiero et al., 2013; Parker et al., 1997).

The **sixth chapter** of this thesis describes a study that relates brain characteristics of ECT treated patients to outcome, after 7-12 years. MTA, WMH and GCA are associated with depression, mild cognitive impairment, and dementia and may represent a common underlying mechanism of these diseases. We therefore hypothesized that patients with severe MTA, WMH or GCA are at risk to develop cognitive impairment or dementia after ECT.

Follow-up was performed by interviewing patients and their caretakers (proxies). Results showed that 55% of the patients had died at follow-up. The proxies reported signs of cognitive decline in 62% of the patients and the general practitioner confirmed a diagnosis of dementia in 18% of the patients. These reported results are in line with previous follow-up studies after treatment of depression with ECT (Brodaty et al. 2000) or with pharmacotherapy (Stek et al. 2002). In disagreement with our hypotheses, a significant association between MTA, WMH or GCA and cognitive decline or dementia was not observed.

Remarkably, in comparison with patients without psychotic symptoms, patients with psychotic symptoms showed significantly less cognitive decline after ECT, as measured with the IQCODE at follow-up. Patients with (versus without) psychotic symptoms had trend-significantly less GCA. Although follow-up was performed in a relative small sample, these results lead to the assumption that patients with psychotic depression are relatively protected against further cognitive impairment.

Finally, results showed a significant association between moderate or severe WMH pre-treatment and a shorter lifespan after treatment (till death), in line with results of previous studies (e.g., Ovbiagele et al., 2006). Patients with moderate to severe WMH may have died before dementia had developed.

Methodological considerations

The studies reported in this thesis should be interpreted in the light of their strengths and limitations.

A strength of all five studies is that they were conducted in two naturalistic cohorts of patients with severe late life depression, recruited at specialized old age clinical facilities, which resulted in samples that strongly represent clinical practice. Therefore, the data described in this thesis can be interpreted to the context of clinical practice. A second important strength is that various methods were used to determine different aspects of brain characteristics. The Fazekas and the ARWMC scales were used to assess vascular white matter disease on MRI, the MTA and GCA scales were used to assess atrophy of the brain, VBM was used to determine differences in regional grey matter volumes, and ICA on functional MRI data was used to evaluate resting state networks. The use of these different methods have expanded our knowledge of factors influencing ECT response. A third strength is that, besides cross-sectional studies, a naturalistic longitudinal study evaluating the relation between brain characteristics and long-term follow-up is described in the last part of this thesis. A fourth strength is that relatively large sample-sizes of patients were included in the studies.

The studies are not without limitations. One possible limitation is the use of different ECT methods. In the studies described in the second, third and fourth chapter, an age dosing protocol was used to define the initial dose of electric current, while in the study described in the fifth chapter, a dose titration protocol was used to determine the initial dose of electric current. The implications of the use of an age dosing protocol might be that older patients receive relatively high doses of electric current, potentially associated with increased response and increased risk of cognitive impairment. Another possible limitation is that the use of concomitant medication during ECT may have influenced the results. Due to the naturalistic setting of the cohorts, patients were allowed to continue medication during ECT. Even though only small groups of patients used psychotropic medication in both cohorts we cannot rule out the effect of medication on the efficacy of ECT, brain volumes, or resting state networks. However, in the fourth study of this thesis, our analyses were corrected for the use of medication and the MRI results did not change. Third, the use of MRI and fMRI scans may have led to a selection bias, because the patients were not allowed to move during the scanning and patients

with severe agitation were therefore excluded. This resulted in varying numbers of patients in the analyses of the second chapter of this thesis. In the second chapter missing data were imputed with the highest scores of MTA, GCA or WMH and results did not change. In addition, a smaller number of patients was included in the study described in the fourth chapter, as VBM is hampered by movement artefacts. Fourth, cognitive status was assessed before study entry and patients with dementia were excluded from both cohorts. However, the inclusion of patients with a prodromal stage of dementia cannot be ruled out. Fifth, the study in the sixth chapter of this thesis includes a naturalistic follow-up of the first cohort. A naturalistic design of follow-up has limitations, because risk of cognitive impairment could have been influenced by unknown factors such as co-morbidity or substance abuse. Furthermore, 19.7% (n= 15) of the patients refused to participate in the follow-up study, due to unpleasant memories (n=11) or current disease (n=4) and 28.9% of the patients (n=22) could not be contacted. Finally, in the studies described in this thesis, cognition was evaluated with the MMSE scores before, during, and directly after ECT and with the IQCODE at follow-up. Both measurements have their limitations. The MMSE is a global measurement of attention, orientation and memory, but does not capture anterograde or retrograde amnesia that may particularly occur after ECT. The IQCODE is a 16-item informant (proxy) questionnaire to detect symptom change over time. The score of the IQCODE reported in the sixth chapter was based on a telephone interview, which may have resulted in under or overreporting of cognitive performance of patients. However, the predictive value of the IQCODE was studied in a large review, showing a high reliability and the instrument performed at least as well as conventional cognitive screening tests (Jorn, 2004).

The following conclusions can be drawn based on the results of this thesis:

Main conclusions for all symptom profiles

1. Moderate to severe MTA in late life depression is associated with poor response to ECT, but not with cognitive impairment after ECT.
2. Moderate to severe WMH is associated with transient cognitive impairment during ECT in patients who switch from unilateral to bilateral ECT, but not with cognitive impairment after ECT.
3. Severe WMH in late life depression treated with ECT is associated with increased mortality at follow-up.

Main conclusions for psychotic symptoms

1. In contrast to the relation between MTA and ECT response in the overall group, in late life depression with psychotic symptoms, moderate to severe MTA is not

associated with poor ECT response. However, more ECT sessions are needed to achieve a response.
2. Late life depression with psychotic symptoms showed high ECT remission rates (70%) and is characterized by pre-treatment smaller volume of the left IFG and hypoconnectivity of the frontoparietal network in comparison with patients with non-psychotic late life depression.
3. Late life depression with psychotic symptoms is associated with less cognitive impairment after seven to 12 year follow-up, reported by the proxy with the IQCODE.

Late life depression with psychotic symptoms

Late life depression with psychotic symptoms is characterized by mood-congruent delusions and/or hallucinations and is one of the most severe forms of depression, showing high relapse rates and a high percentage of admissions to specialized old age clinical facilities. Remarkably, research focussing on this symptom profile is sparse, leading to an ongoing debate whether psychotic depression is a distinct type of depression. Studies in favour of this argument showed that psychotic depression is associated with specific biological abnormalities, such as higher activity of the hypothalamic-pituitary-adrenal (HPA) axis with increased levels of cortisol and increased levels of dopamine (Schatzberg and Rothschild, 1992), as well as neuropsychological deficits related to hippocampal and prefrontal dysfunction (Fleming et al., 2004). Few studies assessed structural and functional characteristics in patients with late life depression and psychotic symptoms.

The current thesis shows that late life depression with psychotic symptoms is a distinct type of depression with, in comparison with non-psychotic depressed patients, significantly higher ECT remission rates, specific structural and functional characteristics, and significantly less cognitive decline at follow-up. Below, I will focus the discussion on these findings in relation to the existing studies.

Structural and functional connectivity in late life depression with psychotic symptoms

In the study described in the fourth chapter of this thesis we showed significantly decreased regional grey matter volume of the left IFG in patients with psychotic symptoms and in the study described in the fifth chapter we showed significant hypoconnectivity of the right frontoparietal network in depressed patients with psychotic symptoms, both compared with non-psychotic depression. These two characteristics may distinguish psychotic depression from non-psychotic depression.

The IFG is involved in cognitive processes related to appraisal of emotional information (Rahko et al., 2010; Liebermann et al., 2004). Regional volume reductions of the IFG have been associated with anxiety in 68 non-depressed patients with anxiety

disorders (van Tol et al., 2010). A task fMRI study in healthy controls showed that the left IFG actively controls the emotional response by inhibiting the amygdala response during active reappraisal of arousing pictures (Johnstone et al., 2007). The fronto-limbic circuit showed to be dysfunctional in patients with depression (Johnstone et al., 2007). Since patients with depression with psychotic symptoms show high co-morbidity with anxiety (Flint et al., 2010), the reported functions of the IFG seem to be specifically relevant for patients with psychotic symptoms in late life depression.

The frontoparietal network includes the dorsolateral prefrontal cortex (DLPFC), the IFG, and parietal regions (Vincent et al., 2008; Shulman et al., 2009) and is involved in cognitive control processes, such as attention and emotion regulation (Ptak, 2012). Previous resting state studies reported decreased connectivity of the frontoparietal network in patients with depression (Kaiser et al., 2015; Hyeth et a. 2015), psychosis (Roiser et al., 2013), obsessive-compulsive disorder (Shin et al., 2014), and attention deficit hyperactivity disorder (Li et al., 2014). This suggests a similar pathophysiological mechanism across mental disorders with impaired cognitive control increasing the vulnerability to develop psychopathology (Cole et al, 2014). Cole et al. (2014) suggested a critical role for the frontoparietal control system in promoting and maintaining mental health as an “immune system of the mind”. This proposed role of the frontoparietal network is in agreement with our finding that significant hypoconnectivity of the frontoparietal network is specifically associated with psychotic symptoms in late life depression. Furthermore, since patients with psychotic symptoms showed high relapse rates after recovery, hypoconnectivity of the frontoparietal network may also be associated with increased risk of relapse after treatment, as observed in patients with chronicity of psychosis (Schmidt et al., 2015).

Follow-up of late life depressed patients with psychotic symptoms

Follow-up of late life depressed patients with psychotic symptoms may provide information on the possibility of psychotic depression being a distinct subtype of depression. In the study described in the sixth chapter of this thesis, we reported an association between psychotic symptoms and absence of cognitive impairment after 7-12 year follow-up. This finding supports the idea of Schatzberg and Rothschild (1992) that psychotic depression is a distinct subtype with a different disease mechanism, possibly resulting in less damage to the brain. Although our follow-up sample was limited and replication is needed, another study showed that patients with psychotic symptoms suffered from shorter depressive episodes (Birkenhager et al., 2003) with shorter periods of increased cortisol and less damage to the brain. Psychotic symptoms have been associated with a higher age of onset of depression (Parker et al, 1992). Since onset of depression starts at a higher age, the risk of cognitive impairment may decrease due to more healthy/preserved years of the

brain. Finally, patients with psychotic symptoms may receive earlier and longer treatment with antidepressants after recovery. Antidepressants may protect patients from developing cognitive impairment and dementia. This premise is supported by a study showing that antidepressants regulate stem cell fate to differentiate into neurons in the adult hippocampus, reduce toxic amyloid peptides, and increase BDNF levels (Kim et al., 2013).

Therapeutic mechanism of ECT

Late life depression with psychotic symptoms showed significantly higher ECT remission rates compared with non-psychotic depression (70.8% versus 38.7%) (chapter four). Structural and functional connectivity characteristics associated with late life depression with psychotic symptoms, may add to the understanding of the therapeutic mechanism of ECT, because high ECT response is possibly related to specific biological characteristics.

MTA and ECT response

A recently published meta-analysis showed that longer (and repeated) depressive episodes and medication failure at baseline are robust predictors of poor ECT response (Haq et al., 2015). Furthermore, longer (and repeated) depressive episodes and medication failure have been associated with increased levels of cortisol, decreased levels of BDNF (Duman et al., 2006) and MTA (Schmaal et al., 2015). These results are in support of those described in the second chapter showing a significant association between MTA and poor ECT response in patients without psychotic symptoms. MTA in patients with psychotic symptoms did not show an association with worse ECT response, but more ECT sessions were needed to achieve a response.

Successful upregulation of BDNF levels in the medial temporal lobe (MTL) may play an important role in the antidepressant mechanism, because BDNF increases neuronal sprouting in the medial temporal lobe and frontal cortex and consequently improves synaptic connectivity of mood regulating neural circuits (Duman et al., 2006). Associations between increased levels of BDNF protein and ECT were reported in rodents (Vayda et al., 1999; Altar et al., 2003), and in depressed patients (Scott, 2011; Bouckaert et al., 2014). In support of MTL involvement in the therapeutic mechanism of ECT are the results of an experimental animal study (Nordgren et al., 2003) that demonstrated a window of transient upregulation of BDNF and downregulation of molecules stabilizing synaptic structures and preventing calcium influx in the MTL of rats after treatment with a single electroconvulsive seizure. In depressed patients numerous studies showed a significant association between volume increase of the MTL and ECT response (Dukart et al., 2014; Joshi et al., 2015; Abbott et al., 2014; Nordanskog et al., 2010; Ota et al., 2015). Two other studies did not show a

significant association between MTL volume increase and ECT response (Bouckaert et al., 2015; Jorgensen et al., 2015) which may be explained by heterogeneous patient groups, use of concomitant medication, or assessment of regional volumes after a window of structural plasticity (Nordgren et al., 2003).

Based on these results, I speculate that severe atrophy of the MTL hampers effective treatment with ECT due to decreased ability of the MTL to increase BDNF levels and decreased ability to increase permeability of calcium channels. In patients with severe MTA this hampered therapeutic mechanism may be partly compensated for by another therapeutic pathway initiated in the prefrontal cortex (see first pathway of ECT mechanism on page 8).

IFG and ECT remission

The results from the study described in the fourth chapter of this thesis indicate that pre-treatment decreased regional volume of the right IFG relates to a significant faster ECT response, i.e. patients with smaller volume of the IFG needed less ECT sessions to respond to ECT. The IFG is involved in cognitive processes related to appraisal of emotional information (Rahko et al., 2010; Liebermann et al., 2004). In addition, a study of Acevedo et al. (2014) showed that increased connectivity of the IFG was associated with positive emotions. Recovered function of a pre-treatment dysfunctional IFG might add to a fast response, especially in the patients that show abnormalities in this brain region prior to treatment. A study in depressed adults treated with antidepressants reported a significant correlation between decreased depression severity and normalized metabolism of the IFG (Brody et al., 1999). SPECT studies showed increased perfusion of the right frontal cortex, during right unilateral ECT-induced seizures in depressed patients (Blumenfeld et al., 2003; McNally and Blumenfeld, 2004) and Heikman et al. (2001) showed that left and right frontal theta activity measured with whole-scalp magnetoencephalography correlated positively with fast ECT response (after four sessions). In addition, results of a task fMRI study in healthy controls showed strong functional connectivity between the IFG and the DLPFC, another brain region that's crucial for emotion regulation (Morawetz et al., 2016a). Another task fMRI study in healthy controls showed a core system, consisting of the left IFG, middle temporal gyrus, and inferior parietal lobe, to be crucial for effective emotion regulation (Morawetz et al., 2016b). Taken together, activation and increased connectivity of the IFG, possibly leading to a volume increase of the IFG, may play a crucial role in the therapeutic mechanism of ECT.

Frontoparietal network and ECT

The fifth chapter of this thesis described a study showing decreased connectivity of the right frontoparietal network in patients with late life depression with psychotic symptoms compared with non-psychotic patients.

The frontoparietal network includes the dorsolateral PFC, the IFG, and parietal regions (Vincent et al., 2008; Shulman et al. 2009) and is involved in cognitive control processes, such as attention and emotion regulation (Ptak 2012). Activation during ECT has shown to be most prominent in the prefrontal and temporal regions (Enev et al., 2007; McNally et al., 2004). Increased activity of this network may be related to increased cognitive control and emotion regulation. Several studies evaluated functional connectivity in relation to ECT response using different techniques in heterogeneous patient groups. Results support involvement of increased connectivity of the dorsolateral PFC (Abbott et al., 2013) and dorsomedial PFC (Leaver et al., 2015; van Waarde et al., 2015) in the response mechanism of ECT. In a functional connectivity study using cortico-cortical evoked potentials to study networks in the brain, results showed that activation of the PFC induces response in the medial PFC and the premotor areas, leading to increased activation of the frontoparietal areas (Enatsu et al., 2015).

These findings support the involvement of the frontoparietal network in the therapeutic mechanism of ECT. Stimulation of the prefrontal cortex may lead to increased connectivity of the frontoparietal network.

Proposed therapeutic mechanism of ECT

In conclusion, I propose two important pathways of the therapeutic mechanism of ECT:

First pathway: ECT directly increases neuronal activity in the frontal regions and may particularly stimulate the IFG. Stimulation of the IFG leads to increased connectivity within the frontoparietal network, resulting in improved cognitive control and emotion regulation.

Second pathway: the temporal cortex is stimulated during ECT resulting in activation of the temporal subcortical structures, i.e. the amygdala and the hippocampus, leading to downregulation of factors inhibiting axonal sprouting and upregulation of BDNF that enhances axonal sprouting in the medial temporal lobe and in the prefrontal cortex and consequently improves synaptic connectivity of mood-regulating circuits. Both pathways may be particularly effective in patients with psychotic symptoms as these patients show neuropsychological deficits related to hippocampal and prefrontal dysfunction (Fleming et al., 2004).

Future directions

To further evaluate the hypotheses described above, larger studies with better defined patient samples are needed. A collaboration between specialized old age clinics will provide the opportunity to pool clinical and biological data of patients with severe late life depression with different symptom profiles. Symptom profiles need to be defined based on strict clinical features. These data can be analysed using a machine learning approach that establishes, based on a data-driven way, the importance of all clinical and biological characteristics of patients in relation to successful ECT response.

To evaluate the hypothesized therapeutic mechanism of ECT, I propose a large study that evaluates functional connectivity patterns of resting state networks before and after ECT in relation to response to ECT, especially in patients with late life depression with psychotic symptoms and in relation to speed of ECT response and relapse after ECT.

Clinical recommendations

Late life depression with psychotic symptoms is a severe, life-threatening disease with high admission rates to specialized old age clinical facilities. Since ECT shows fast and high remission rates in patients with late life depression and psychotic symptoms, ECT should be considered at an early stage of the disease. Moreover, clinicians should be aware that patients with psychotic symptoms and severe MTA need more ECT sessions to achieve a response. Clinicians should inform patients with severe MTA and their relatives about the longer duration of treatment that is needed to achieve response.

In all symptom profiles of late life depression the presence of WMH does not diminish the likelihood of response to ECT. In the case of patients with WMH who switch to bilateral ECT, it may well be possible to better prepare patients and their relatives to cope with transient cognitive impairment and to acknowledge the fact that these disturbances in cognition will improve when ECT is continued.

Finally, pre-treatment WMH increase the risk of mortality after long-term follow-up. This emphasizes the importance of adequate treatment of co-morbidity such as cardiovascular disease and diabetes mellitus, since WMH is strongly associated with these disorders (Alosco et al., 2013, Reinhard et al., 2012).