Chapter 8. Concluding Remarks and Future Research Directions

The goal of this thesis was to demonstrate that brain perfusion SPECT can help to clarify important issues regarding the prodromal MCI stage of AD and relapsing NMO. Specifically, this thesis shows:

1. That based on recently published literature, brain perfusion SPECT is a valid biomarker of neuronal injury in MCI due to AD in both clinical and research settings, equivalent to FDG-PET but less expensive and more accessible worldwide (Chapter 2).

2. That brain perfusion SPECT combined with graph theoretical analysis can reveal subtle (early) network-related cerebrovascular reactivity (CVR) alterations in MCI, which are not detected by the current standard analysis (Chapter 3). The alterations found involve brain regions directly related to cognitive dysfunction in MCI, which could have significant implications for early diagnosis and treatment of AD.

3. That graph theoretical analysis of brain perfusion SPECT data of amnestic MCI patients shows an inverse association between the episodic memory and the patient contribution to the global modularity of the CBF correlation network (Chapter 4). This finding highlights the potential of graph theoretical analysis to develop a CBF connectivity-based biomarker for MCI at the individual level, since episodic memory decline is the hallmark and major symptom of MCI patients that progress to dementia.

4. That in MCI, as compared to controls, the global modularity of the CBF correlation network is increased while the global efficiency is decreased, both at baseline and after one-year follow-up (Chapter 4). However, no significant changes in the MCI group network at baseline, as compared with one-year follow-up, are found which suggest that one year may not be enough to properly address the temporal evolution of the CBF correlation network in MCI.
5. That the MMSE of amnestic MCI patients, similar to episodic memory, also shows an inverse association with the patient contribution to the global modularity of the CBF correlation network but only at one-year follow-up (Chapter 4). These findings support that the global modularity could be associated with alterations in other cognitive domains that become relevant to the patient as the disease progresses since the MMSE reflects cognitive function globally (not only episodic memory impairment).

6. That voxel-based analyses of brain perfusion SPECT and structural MRI data identify changes in brain perfusion and structure behind the ON attack-related process in relapsing NMO (Chapter 5), which could be relevant for the comprehension of incremental visual disability in this disease. Furthermore, these findings provide evidence that brain microvasculature is an early disease target and suggests that brain perfusion alteration could be important in the development of brain structural abnormalities in relapsing NMO.

7. That the number of ON attacks per patient is a potential confounder when comparing relapsing NMO patients with controls using voxel-based statistical analysis of both brain perfusion and tissue volumes (Chapter 6). This finding provides a new methodological insight that could be useful for future clinical neuroimaging studies, including brain perfusion SPECT, in relapsing NMO.
On the basis of the findings presented in this thesis, the following possible future research directions are recommended in the addressed topics.

**Future research directions based on the findings of Chapter 2.** Further cost-effectiveness analyses are necessary to compare brain perfusion SPECT and FDG-PET with structural and advanced MRI and other neuronal injury biomarkers in MCI due to AD for both clinical and research application.

**Future research directions based on the findings of Chapter 3.** First, to further clarify some results at the regional level, it may be necessary to increase the number of subjects and/or to use a more potent vasodilatory challenge in future studies. Second, although the individual patient analysis was addressed in Chapter 4, it was only performed at the basal condition (i.e. no vasodilatory challenge was used). Therefore, future studies should be based on the individual level in order to examine the association between network-related CVR alterations and clinical cognitive data. In fact, the study presented in Chapter 4 was the first step in this direction to establish the validity of the methodology used in a simpler case such as the basal condition. Third, longitudinal studies are needed to investigate the temporal evolution of the CBF correlation network along the continuum from normal aging to AD dementia. This issue was also addressed in Chapter 4 but again, only for the MCI group network and didn’t include the vasodilatory challenge. Actually, only 65 percent of MCI patients studied in Chapter 3 (CVR study) had a follow-up SPECT scan. Four, possible artificial negative correlations due to the inclusion of the global CBF as a confounding variable (during the construction of the CBF correlation network) should be investigated in future studies.
Future research directions based on the findings of Chapter 4. First, the next step in developing a CBF connectivity-based biomarker at the individual level in MCI must take place through methods based on regional network metrics rather than global metrics. The brain network underlying the episodic memory involves specific brain regions rather than the entire brain. Second, the temporal evolution of the CBF correlation network in MCI (at the basal condition or together with the vasodilatory challenge) should be addressed in longer longitudinal studies. Third, in future follow-up studies, other cognitive domains should be evaluated as well (not only episodic memory), especially in patients with more advanced stages of AD. Four, although most of our MCI patients could evolve to AD dementia, with an intermediate level of certainty according to the latest diagnostic criteria for MCI due to AD [1] (see also supplementary data presented in Chapter 3), we cannot exclude the possibility that some of our MCI patients evolve to another type of degenerative dementia as MCI is a complex heterogeneous condition. Therefore, some of the suggested explanations need further validation in MCI patients with confirmed AD pathology.

Future research directions based on the findings of Chapter 5. First, future studies using more sensitive NMO-IgG assays (second generation) are needed to clarify the association between white matter perfusion changes (ON attack-related) and NMO-IgG status. Second, our main findings should be replicated in longitudinal studies, including both acute relapse and stable phases of the disease in NMO subjects with confirmed NMO-IgG positive status. Considering the uncommonness of NMO, a multicenter study would be the most appropriate approach.

Future research directions based on the findings of Chapter 6. More studies in other and larger populations of relapsing NMO patients are necessary to further clarify the confounding effect of the number of ON attacks per patient, including the use of other thresholds for grouping patients according to the number of ON attacks.
As a final remark, other brain perfusion neuroimaging technologies can be used to study the same neurological disorders addressed in this thesis, which include PET (using various tracers), Xenon enhanced CT, dynamic perfusion CT, MRI dynamic susceptibility contrast, arterial spin labeling, and Doppler ultrasound. Nevertheless, each of these technologies have advantages and disadvantages [2].

The major disadvantage of brain perfusion SPECT is its lower spatial resolution as compared to PET, CT, and MRI-based technologies. SPECT spatial resolution, however, seems to become substantially improved. In 2015, a new SPECT system (G-SPECT) was presented at the World Molecular Imaging Congress that allows for less than 3 mm spatial resolution (an improvement of about 3 folds, compared to the standard SPECT), with a low dose and fast imaging, comparable to the modern PET technology (https://www.itnonline.com/content/breakthrough-spect-technology-wins-commercial-innovation-year-wmic-2015). This new SPECT system was awarded as the innovation of the year by the World Molecular Imaging Society. Basically, this new SPECT machine is a translation of micro-SPECT technology into a clinical instrument.

Moreover, the recent novel iterative algorithms for image reconstruction and methodologies to correct physical problems affecting SPECT significantly improved image quality and promise a great impact of this technology [3, 4]. Not less important are the new approaches to extract relevant information from the brain perfusion SPECT images, such as applying the graph theoretical analysis to study brain connectivity (e.g. Chapters 3 and 4). All these advances could positively impact the role of brain perfusion SPECT in neurological disease research, particularly, in further investigations of the vascular component of the pathophysiological complexities of MCI and relapsing NMO.

Furthermore, in the broader context of neurosciences, the current trend is the integration of data from multiple non-redundant neuroimaging modalities facilitates the investigation of
complex pathological processes where the interaction between function and structure of the brain is key to better understand these processes [6]. Although more research should be done, an example of this integration is the study presented in Chapter 5. This integrative principle is potentially applicable to any method of image analysis, including network-based analyses such as the graph theoretical analysis of the CBF correlation network presented in Chapters 3 and 4. For example, it would be interesting to study the interaction (and integration) of the CBF correlation network with structural brain connectivity based on diffusion tensor imaging data in the same MCI patients.

As indicated in the introduction of this thesis, the ultimate goal of these efforts is to substantially improve the diagnostic accuracy and medical care of patients, especially in the early stages of disease where there may be more possibilities to stop or slow down the pathological processes.

In conclusion, the findings presented in this thesis show that brain perfusion SPECT can help to clarify important questions regarding the prodromal MCI stage of AD and relapsing NMO, which could have significant clinical implications and, therefore, the potential for practical applicability. Moreover, our findings warrant further research in these two complex diseases where recent advances in SPECT technology could also have a positive impact.
References


