Neuroimaging in dementia.

Functional and structural neuroimaging in dementia was thoroughly reviewed in two papers resulting from the last CCCD conference, which were published in 2007 [1, 2]. Since then, the field has grown rapidly not only because the roles of techniques discussed at that time has been further refined, but also as a result of the deployment of new strategies such as *in vivo* amyloid imaging, which have substantially added to our understanding of neurodegenerative diseases and changed the way we look at diagnosis. Those approaches have been instrumental in the development of new diagnostic criteria for Alzheimer's disease, in particular in its early-clinical (pre-dementia) and even pre-clinical phases.

This review article will cover those developments and will strive to follow up on the two previous papers in providing Canadian practitioners with recommendations on the use of neuroimaging in the evaluation of patients with cognitive impairment as of 2012.

Any paper on diagnosis in dementia has to start by asking whether coming up with a proper diagnosis (by whatever means) is worth the effort. To many, identifying one test or another as a good or poor way of establishing a diagnosis is moot if clinical management is not ultimately affected. And, for many, the current therapeutic armamentarium being quite limited in the field of dementia (but see other papers from this conference on therapy), it might appear that the investment is hard to justify. This of course involves in part some difficult to quantify issues, such as the patients' and their families right to know about their condition and its prognosis, which are necessary elements in discussions on what practical measures, if any, should be taken in the future to ensure that the situation doesn't get out of control. Also, there is some evidence that early diagnosis, in particular when performed with functional imaging, is actually a wise economic choice, especially with Positron Emission Tomography (PET) but also possibly and to a lesser extent with Single Photon Emission Computed Tomography (SPECT) [4, 5, 6].One could also argue that identifying the disease underlying cognitive deterioration is useful in ruling out reversible causes, although this is probably overly optimistic, as suggested by a relatively recent meta-analysis [7]. Still, recent reviews strongly suggest that the use of acetylcholine esterase -nhibitors , especially if introduced early on, is associated with slower deterioration of subjects with Alzheimer's disease (AD) [8]. The recommendations that will be made in this article will therefore assume that establishing the cause of a dementing process is a reasonably useful clinical proposal.

An important factor to take into account when discussing the imaging diagnosis of neurodegenerative diseases is that it very generally rests on recognition of patterns deemed to be more or less specific for a given condition. If such a pattern, associated for example with AD, is found with an imaging modality (whichever it is being moot), then the odds of that disease being present are increased. However, neurodegenerative diseases are all associated with ageing, and the probability of finding any of them in a patient as an isolated process decreases with increasing age (for a review of this, see [3,]). Therefore, finding a "pure" disease-related pattern is likely to become less and less probable as patients more advanced in age are evaluated (and there might even be a gender effect for this [9]), a fact well established by the difference in presentation on functional imaging with PET-Fluor-18 fluorodeoxyglucose (^{18}F-FDG) of early-onset as compared to late-onset AD [10, 11, 12, 13]. Moreover, the relationship between dementia and certain parameters evaluated by imaging might vary

significantly with age: it would appear that amyloid load, for instance, might not be as specific for cognitive impairment in very old patients as compared to younger ones, whereas indices of neuronal loss (volumes of cortex or hippocampus, and presumably metabolic activity or absolute blood flow of those same structures) might show a more stable relationship to dementia across ages [14]. Recommendations on the use of imaging techniques will therefore have to be interpreted in light of such plausible (although not nearly established) factors.

The next sections will review different imaging modalities as applied to the evaluation of subjects with cognitive deterioration. Some of those modalities have been in use for a significant period of time and have been the subject of relatively extensive reports, while others are clearly more experimental but offer enough promise to warrant a discussion of their potential, if only because some subjects with unusual presentations might occasionally benefit from their use. Other imaging modalities do of course exist, but are currently too far from clinical implementation for their use to be fruitfully discussed here.

1) PET ^{18}F-FDG, SPECT cerebral blood flow and other SPECT techniques

The present review was based on a PubMed search for articles including keywords PET-and-FDG-and-Alzheimer, ADNI and Alzheimer's Disease Neuroimagin Initiative, and SPECT-blood flow-and-Alzheimer, from January 2007 to December 2011 (i.e., after the period covered in the previous position paper from the 3rd CCCD). Of the 208 articles that came out for the PET part, and 98 for the SPECT search, those that were written in French or English were submitted to a screen favoring, but not limited to, review articles, as well as those felt to bring new light to recommendations from the last CCCD. Articles published prior to that period also have been referred to when deemed useful, as were articles on other forms of dementias. Some papers from early 2012 that were considered to significantly impact the present discussion were also reviewed.

The consensus that emerged from the 2006 CCCD on the role of PET ^{18}F-FDG and SPECT regional cerebral blood flow (rCBF) imaging was that there was "fair evidence" that those techniques could be useful to specialists in establishing a specific diagnosis of the cause of dementia (in particular in distinguishing AD from FTD). It was also recognized however that there was a significant level of variability in local expertise in interpreting results, which significantly impacted their usefulness. That position was quite new as compared to the then, and still, current guidelines of the American Academy of Neurology (AAN) for dementia, which only recognize a role for structural neuroimaging [15]. Those guidelines however do look quite dated in light of more recent pronouncements from the European Federation of Neurosciences [16] and from the National Institute on Aging and Alzheimer's Association (NIA-AA) [17, 18, 19]. Interestingly, the main author of the AAN Guidelines is a co-author of the recently published NIA-AA criteria. The present article will revisit those different issues.

a) PET ^{18}F-FDG *vs.* SPECT rCBF: General considerations

PET imaging of ^{18}F-FDG distribution is known to be a reliable way of evaluating regional cerebral rates of glucose utilization (rCMRGluc), whereas SPECT imaging with either ^{99m}Tc-HMPAO or ^{99m}Tc-ECD, the two most frequently used agents for rCBF measurements, is well established for assessment of that parameter. It is further recognized that, at least under normal conditions, rCBF and rCMRGluc are tightly coupled to one another [20] and that they both represent the regional “intensity” (a combination of synaptic density and unit activity) of glutamatergic neurotransmission [21]. Therefore, physiologically at least, these two techniques can be considered to be largely equivalent. This doesn’t mean that such equivalence will hold under any circumstance, and neurodegenerative processes likely can affect either cerebral oxidative metabolism or cerebral perfusion independently [22, 23, 24, 25].

Because of that physiological equivalence, the distribution patterns seen in neurodegenerative disorders as established over close to 30 years of use of those techniques (the first reference that could be found for dementia and PET ^{18}F-FDGdates back to 1982, and for dementia and SPECT to 1984, [26, 27]) are largely the same for PET ^{18}F-FDG and SPECT rCBF studies (whether one uses ^{99m}Tc-HMPAO or ^{99m}Tc-ECD, the two tracers available for SPECT rCBF evaluation); a review of those well-known patterns is beyond the goals of this article. However, it also means that both approaches are subject to similar effects linked to age (see above) and to the influence of cerebral reserve [28], an important clinical concept which has a direct influence on the interpretation of blood flow or metabolic deficits intensity one should make when looking at studies from subjects with differing levels of education, and possibly even from males as compared to females, as males have been suggested to show more brain reserve than females [29, 30, 31, 32, 33].

From a technical perspective however, the two approaches differ quite significantly in a number of ways. PET imaging has a strong advantage over SPECT in terms of spatial resolution, allowing for better quantification of activity (and therefore of the physiological parameter being measured) in the brain. This is clinically important because it directly translates in the ability to pick up milder, earlier alterations linked to disease. Although performances will vary, a typical PET system will image fluor-18-labeled radiotracers with a spatial resolution on the order of 4 to 5 mm, whereas most SPECT systems will operate, with technicium-99m agents, at 8 to 12 mm. This is most likely the main reason why comparisons of diagnostic performance from those two techniques systematically show a significant difference in favor of PET, which displays a 15-20% better accuracy [34, 35, 36].

Still, resolution performances are evolving, with in fact less possibilities for improvement with PET as compared to SPECT. Indeed, PET imaging has physical limitations to its ultimate resolution, which is probably close to what the best, brain-dedicated, state-of-the-art scanners (Siemens HRRT for instance) already can achieve (2,5 to 3 mm). In the case of SPECT however, no such fundamental limit exists: in theory, it would be possible to build scanners that would continuously improve, yielding ever lower resolutions. Of course, technological limits will be reached, but there currently are brain-dedicated systems (Neurologica InSpira, for example) with an intrinsic resolution which rivals that of the best PET systems. Because of radiation detection sensitivity problems, those systems do not yet produce images on a par with PET technology, and as only very few centers operate such instruments, their impact on diagnostic performance remains to be established. Another important development leading to improved SPECT imaging is the recent significant increase in the number of CT-coupled SPECT scanners, which

have made attenuation correction (systematically performed in PET studies) of SPECT studies much more routine. It therefore appears likely that the gap in diagnostic accuracy between PET and SPECT will decrease over time. Moreover, expert interpretation in general has been more the norm for PET than SPECT studies in the past [35], but computer assisted interpretation is now widely available and has been shown to significantly impact the quality of SPECT reporting [37, 38]. All in all, SPECT therefore is considered as a valid diagnostic imaging option [39]. At the same time, one of the major advantages of SPECT over PET, i.e. its greater availability and lower cost, is being eroded by the significantly increased availability of PET scanning, driven in large parts by its oncological applications. ^{18}F-FDG distribution networks are now well established in many countries and make it possible to perform PET imaging in centers where only a scanner is available (no cyclotron required), at a cost which is currently competitive with that of other imaging approaches.

Finally, it is important to remember that Nuclear Medicine techniques are minimally invasive, with administration of the radiopharmaceutical for the studies considered here being by simple IV injection. Their track record in terms of side effects is remarkable, with recent statistics citing 0.9 recorded incidents per 100 000 administrations [40]. The long term risk of radiation exposure is that of developing cancer, but given the age of populations being submitted to studies for evaluating dementia, this is of limited concern.

b) SPECT rCBF (and other) studies

As mentioned above, SPECT studies have since the last CCCD recommendations seen some significant technological modifications (more routine attenuation correction, high resolution scanners). However, no clear evidence is available as to the presence of an impact of those developments on the clinical performance of SPECT in dementia. Review articles continue to report on non-attenuation corrected studies and come up with numbers for diagnostic accuracy that are of the same order as those cited in 2007: pooled sensitivity and specificity reported around 75 and 90% respectively [2], with higher sensitivity in a more recent paper however, still lower than with PET (82% *vs* 93%) [36].

Various recent papers have evaluated the ability of SPECT rCBF studies to differentiate AD from other causes of dementia/cognitive impairment. A study using voxel-wise Z-score pattern analysis has confirmed the possibility to differentiate early AD from fronto-temporal dementia (FTD) and pure vascular dementia (VD), but not dementia with Lewy bodies (DLB; but, see below) or mixed AD-VD [41]. Differential diagnosis between FTD and AD is also addressed directly in a paper on 25 FTD and 31 AD cases, all pathologically confirmed, finding that SPECT studies should not be interpreted blindly, but that in combination with clinical data, ^{99m}Tc-HMPAO studies provide supplementary information, and can eventually modify the clinical diagnosis [42]. The differential diagnosis between AD and depression with cognitive impairment appears clearly less optimal, in fact raising a possible direct link between neurodegeneration and depression [43].

A significant body of work about differential diagnosis of dementing diseases with SPECT rCBF has been dedicated to DLB and AD, which is not surprising given the high prevalence of each of those (DLB being

responsible for up to 30% of dementia cases [44]). The presence of occipital hypoperfusion in dementia accompanying Lewy bodies has been known for a long time [45] and has been repeatedly confirmed as a reliable sign to distinguish AD from DLB, including in recent publications [46]. One group has however raised doubts about the value of that sign [47], but that paper remains an outlier from that perspective. Increased perfusion to the striatum is also reported as a sign distinguishing DLB from AD [48, 49]. Still, the reported sensitivity for differentiating DLB from AD with SPECT rCBF (approximately 65% and 80% respectively [39]) might not be optimal.

Non-rCBF studies can also be performed clinically to differentiate DLB from AD with SPECT agents targeting the dopamine cell membrane transporter. Iodine-123 labeled ioflupane has been available commercially in Europe since the beginning of the century, and has recently received clearance from the FDA in the USA (DATScan, GE). Unfortunately, the precursor molecule is a restricted substance which cannot be exported from the USA, and the manufacturer of that tracer has of yet not decided to make it available in Canada. Its usefulness in differentiating DLB from AD is quite impressive (specificity of over 90% based on phase III multicenter clinical data [50], and sensitivity of 88% with a specificity of 100% in a study with histopathological confirmation, as compared to 75% and 42% respectively for clinical assessment [51]). A complete review on the subject has recently confirmed the usefulness of that approach [52]; cases showing unclear results with that agent are likely to represent combined AD/DLB pathology.

Another non-rCBF SPECT approach in that field is based on imaging of the norepinephrine transporter on the plasma membrane of sympathic terminals in the heart, which are lost early in DLB and Parkinson's disease, using the ligand iodine-131 MIBG (metaiodobenzylguanidine). That tracer is approved for human use and commercially available in Canada, and results in small studies have been quite good (above 90% accuracy for the diagnosis of DLB, [53]; see also [54]).

The ability of SPECT rCBF evaluations to predict clinical evolution is discussed by different authors, with variable conclusions. One article indicates that in a group of 84 subjects with AD accrued in 11 different centers, the presence of frontal anomalies in addition to posterior associative cortices defects (as ascertained using the 3D-SSP algorithm) is associated with more severe initial status, and more rapidly progressing disease [55]; the same group confirmed those results on another cohort [56]. However, the possibility to predict conversion from mild cognitive impairment to dementia of the Alzheimer type with rCBF studies is not established at this time. Decreased perfusion in the cingulate gyrus (mid and posterior portions; with increases anteriorly in that structure) have been reported as predictive of conversion [57], as has hypoperfusion in the parahippocampal and inferior temporal regions [58]. A more recent study on 127 MCI and 59 healthy control subjects however has found only marginal power of prediction for conversion using rCBF SPECT studies, mostly from observations of decreased perfusion in parietal and medial temporal areas, which disappeared in logistic regression analysis when clinical indicators were considered [59]. The reason(s) for those discrepant results is (are) not clear: populations and image analysis differences can probably explain some of the differences, but early, preclinical metabolic (and, therefore, presumably rCBF, see above) changes in subjects at high risk for AD [60] have been known to be present for a long time, and more recent observations have shown clear differences of rCBF patterns between MCI sub-types with risks of evolution to AD which are known to be different

[61], suggesting that brain perfusion studies should have some degree of predictive power. One potential confounding factor could well be that medial temporal structures, which have typically been expected to show early blood flow decreases, might in fact behave in a more complex fashion from that perspective, with early above normal values of rCBF during activation despite overall tissue losses [62]. As the evidence for such hyperactivity accumulates [62, 63], it might be that different patterns will be shown to predict risk depending on the exact evolution stage of subjects.

A potentially important issue impacting on the clinical usefulness of rCBF SPECT imaging for dementia assessment is the use of computer-assisted image analysis. Multiple techniques have been and continue to be proposed for differential diagnosis and prognosis purposes. In fact, of all the rCBF articles cited above, only [42] used purely visual analysis of the data (but nevertheless processed all cases with a standardized spatial registration, which is considered by this author to be the minimum required to produce acceptable interpretations). It is virtually impossible to determine from the currently available data whether one approach is better than another, as head-to-head comparisons are not generally available. When they are, differences appear to be limited, although, somewhat worrisomely, they also seem to hinge on rather subtle and difficult to predict technical issues [64]. Obviously, techniques with comparisons to a normal database have to take into account that such databases are radiopharmaceutical-specific, i.e. a ^{99m}Tc-ECD template cannot be used for analysis of 99mTc-HMPAO cases (and of course, the opposite is also true; [65]), meaning that such templates need to be generated for each agent. In fact, many important issues remain to be resolved: should multivariate approaches be used instead of univariate ones [66]? Are such relatively complex approaches, largely unavailable to most clinical centers, necessary in view of good results obtained with more standard software and statistical analysis packages [67]? Methods using non-invasive, absolute quantification of rCBF, now shown to be easy to implement clinically in a reproducible fashion [68], also might be useful [69]. Ultimately however, the most important question is whether such approaches are superior to visual evaluation of adequately spatially registered data. While some authors ([38], [59]) say it is so, others have found visual interpretation to be a valid alternative ([70], [71]). The answer probably needs to take into account the experience of the reader, as shown in [72], where the impact on accuracy was found to be much more significant for less experienced interpreters than for those regularly involved in reporting such studies.

c) PET ^{18}F-FDG studies

As already mentioned, the use of PET ^{18}F-FDG imaging for evaluation of dementia dates back to close to 30 years already, and the accumulated data is quite significant. Numerous reviews of its application for the diagnosis of dementia and the differential diagnosis of the diseases causing it have been published already, reporting on large numbers of subjects, and sometimes expressing some wonderment at the ongoing questioning that the technique faces in that area [73].

While this article was being prepared, a review article was published [74] that covers in a very exhaustive and well-structured fashion the literature on PET ^{18}F-FDG imaging in dementia from the

period beginning in 2000 to the latter half of 2011 (that review was submitted on August 27, 2011, and accepted in revised form on November 3, 2011). The methodology employed is similar to that proposed here, and the conclusion are very close to those arrived at here when covering, in combination with the previous CCCD report on the topic [2], essentially the same material. A summary of that article limited to its imaging-linked sections, with comments, therefore appears to be the best solution to avoid "reinventing the wheel".

The review article concentrates on articles publishing results on PET ^{18}F-FDG imaging in dementia that meet recognized standards to allow for valid conclusions about usefulness to be drawn, a condition that has not often been met in previous articles. The authors identified 11 studies using such criteria. Those studies cover hundreds of subjects (the exact number is difficult to specify as some cohorts come from the same centers and therefore likely contain some of the same patients) classified, based on different diagnostic criteria including autopsy results, clinical follow-up or clinical assessment, as AD, healthy controls, or bearers of other conditions (depression, cerebral vascular disease, neurodegenerative conditions other than AD, including DLB,FTD, VD, progressive supranuclear palsy (PSP), and Parkinson's disease (PD)). Some were multicenter studies, and some were from primary care centers, others from more specialized care centers. All studies involved visual evaluation of PET imaging, with or without added computer-assisted diagnosis.

From the 5 case-control studies reviewed, all at American Academy of Neurology diagnostic evidence level III, pooled sensitivity, specificity and accuracy for the diagnosis of AD were respectively 96%, 90% and 93%. From the 2 longitudinal studies, sensitivity results were 78% and 91.7% for the presence of dementia, with specificities of 81% and 88.9%. For the 2 pathology-controlled studies looking at the presence or absence of AD, sensitivities were 94% and 84%, and specificities 73% and 74%. PET ^{18}F-FDG imaging is also very good at differentiating AD from other conditions which can result in dementia, with sensitivities ranging from 78% to 97%, specificities from 74% to 86% and accuracies from 79% to 93%.

Such numbers allow physicians to increase their confidence in the diagnosis given to a patient above the level associated with a purely clinical approach. An important paper referenced in the review article [75] shows that diagnosis is helped significantly in over 70% of cases in a memory clinic setting, with 28% of studies only being noncontributory. Furthermore, at least 2 other references (not just the one mentioned) establish that a negative PET study has a very high predictive value for the absence of clinical progression in the years following the test [76, 77].

The controversial role of hippocampal evaluation for the diagnosis and for predicting evolution of AD and other neurodegenerative diseases is again raised for PET studies, as it was for SPECT rCBF imaging. Most results on that issue come from the same group [78], with admittedly strong observations [79], including pathologically verified diagnosis, and with similar observations from other authors also [80]. Still, just as is the case for SPECT studies (see above), hippocampal anomalies as a distinctive sign of AD remains controversial [74], probably at least in part because of the reasons already alluded to [62], as well because of issues of specificity [74] for AD when compared to other neurodegenerative diseases. In fact, again, questions have been raised as to possible early metabolic hyperactivity of the medial temporal structures during cognitive activation in pre-dementia subjects [81]. Technical improvements

in evaluating ^{18}F-FDG uptake in the hippocampus might allow for clarification of that issue in the future [82], and the possibility that apparently decreased hippocampal metabolism in AD might be related to partial volume effects cannot be discounted [83].

Predicting clinical evolution from PET ^{18}F-FDG studies in patients with cognitive disorders remains an important clinical objective. Clinical identification of non-demented patients at risk of evolving to AD in general involves recognizing the presence of amnestic mild cognitive impairment (aMCI). Still, not all aMCI evolve to AD, remaining stable or developing other neurodegenerative conditions [84], but early intervention in AD cases is well recognized as being important [8, 85]. The review article just discussed avoids commenting on the value of this technique as applied to MCI, mostly because of difficulties in interpreting studies using difficult to compare definitions of that state, or concentrating only on aMCI and thereby considered to be of limited clinical interest as those represent only a fraction of MCI cases. Nevertheless, work cited above [76, 53] indicates that a normal PET study strongly reduces the risk of cognitive deterioration for a number of years. Also, subjects at high risk for developing AD and members of families with hereditary forms of AD have been known for many years to harbor, before they show any evidence of cognitive deterioration, changes on PET ^{18}F-FDG studies which are comparable to those from AD subjects with AD [86, 87], and the presence of beta-amyloid in the brain of non-demented subjects is associated with abnormal ^{18}F-FDG accumulation in the posterior cingulate and temporal lobes years before they show cognitive decline [88], suggesting that such a pattern should indeed carry prognostic information. While the objections of the authors of [74] to commenting on the usefulness of PET imaging in MCI are not unreasonable, publications are reporting in aMCI, i.e. in patients at high risk of evolving to AD, a pattern of PET ^{18}F-FDG anomalies which more or less fully recapitulates that seen in AD [89] or might suggest other underlying conditions [90]. Clinical follow-up of aMCI or even pre-aMCI subjects shows that the initial ^{18}F-FDG study is indeed a strong predictor of conversion to AD or cognitive decline [91, 92, 93, 94]. ^{18}F-FDG might in fact be one of the better AD biomarkers in terms of its ability to follow cognitive decline throughout the course of the disease [95, 96]; a recent meta-analysis on that subject found better performance for this by PET as compared to SPECT rCBF and structural MRI [97], a topic which is however not settled yet [98].

The relative roles of PET and CSF biochemical measurements in the diagnosis and prognosis of AD is also difficult to establish at this time, with limited and variable data having been published [99, 100].

Overall, the potential role of PET ^{18}F-FDG studies as a marker of risk for evolution to AD dementia in preclinical/early clinical subjects has been reviewed in detail by authors from a group with widespread experience in that field, and is recognized as a useful approach, a positive pattern of glucose utilization in subjects with MCI predicting evolution to overt AD in 75-100% of cases. The same group does recognize that improved specificity in that domain might come from supplemental information provided by beta-amyloid PET imaging [101, 102, 103]. Given the relatively high likelihood that different biomarkers will have a performance that will vary depending on the exact phase of the pathological process, a combination of such markers (imaging and non-imaging) might have a better performance than any single one in terms of diagnostic accuracy [104, 105], but the economic tolerability and usefulness of using many of those tests is not known at this time.

A practical issue arising from the previous discussion is that of the value of repeated imaging when a PET study is interpreted as normal or inconclusive for the presence of a dementing process, in particular AD, in a patient clinically suspected of having such a disease. Very little information is available in that area, but should a second attempt be performed with PET, the results from one group suggest that an absence of progression over one year is unlikely to be associated with the presence of an active neurodegenerative process such as AD [106]; that observation also has implications as to the possibility of using PET ^{18}F-FDG imaging to increase the statistical power of studies evaluating the effects of potential therapeutic interventions.

Other diseases can present with cognitive impairment aside from the more frequently discussed ones that are AD, FTD and DLB. In fact, PSP has already been mentioned above, and is part of a group of diseases often designated as “Parkinson +”. Patients affected by those diseases are sometimes referred for evaluation of their cognitive decline. Although the literature is much more limited on that topic than it is for other neurodegenerative conditions affecting cognition, there is evidence that specific brain metabolism patterns can be seen with PET ^{18}F-FDG imaging [107, 108]

Another practical issue for ^{18}F-FDG studies evaluation is, just as for SPECT, that of computer assisted interpretation. The number of techniques that have been proposed in that field is staggering, with some of those having achieved significant acceptance [109]. Those techniques fall under two general headings, one where a T- or Z-map is generated, often using the Statistical Parametric Mapping (SPM) analysis package for image processing (see for instance, amongst many others in that category, [110, 111, 112]), and one using some variation on Principal Component Analysis (see for instance [113, 114]). Numerous technical issues remain to be settled when using those methods of analysis, including the minimal size (and, in fact, nature) of the reference population being used for comparison purposes [115] (but it is also possible to bypass that problem altogether by using purely internal references [116]) and the region of interest to be used for normalization purposes when comparing subjects to reference populations (see for instance [117, 118, 119]. In general, the same principles seem to apply here as were already discussed for SPECT, i.e. such approaches seem to be particularly clinically helpful when used by observers with limited experience (clinical visual interpretation of those tests being subject to significant variability [120]) or in research settings [121].

RECOMMENDATIONS FOR CLINICAL USE OF SPECT/PET IMAGING IN SUBJECTS WITH COGNITIVE DISORDERS

Any clinical decision as to whether imaging with PET ^{18}F-FDG or rCBF or another SPECT technique is warranted in a patient with cognitive impairment can only be made in a context where standard clinical, laboratory and non-quantitative structural assessments (CT or MRI) have already been

performed and have not yielded a diagnosis considered to be sufficiently reliable to establish a valid prognosis or a therapy strategy.

1) If such conditions are met in patients with cognitive impairment that is compatible with dementia, PET ^{18}F-FDG imaging can establish the presence or absence of a pattern of abnormal brain glucose consumption associated with one of several neurodegenerative diseases with high sensitivity and specificity. This can help define what type of pharmaceutical therapy can be efficiently and safely administered to the subject, as well as to establish the likely rate of progression. Use of PET ^{18}F-FDG imaging is therefore recommended for such cases.
2) If PET ^{18}F-FDG imaging is not practically available when dealing with such cases, consideration should be given to imaging rCBF distribution with SPECT, which is generally widely available in Canada. Performance in terms of diagnostic accuracy would however be expected to be lower than with PET ^{18}F-FDG.
3) If such conditions are met in patients with cognitive impairment that is compatible with MCI, and consideration is being given to introduction of a specific medication (choline esterase inhibitor for instance), or if the patient or her/his physician have a need for increasing the accuracy of prognosis, again, PET ^{18}F-FDG imaging can establish the presence or absence of a pattern of abnormal brain glucose consumption associated with one of several neurodegenerative diseases with high sensitivity and specificity. However, the less advanced the patient's condition is, the less sensitive that type of imaging will be, although there is evidence that PET ^{18}F-FDG can show evidence of abnormal brain metabolism years before symptoms become evident in certain patients. Use of PET ^{18}F-FDG can be recommended for such cases, under the circumstances mentioned above
4) Again, if PET ^{18}F-FDG is not available, consideration should be given to performing rCBF SPECT imaging as a second choice.
5) PET ^{18}F-FDG imaging can be used in order to help establish a clinical diagnosis in subjects with atypical presentations of cognitive deterioration, i.e. those with movement disorders for instance. Although the exact diagnostic accuracy of that approach is not well established, those cases often present diagnostic challenges to neurologists, very little diagnostic approaches are available, and a correlation of clinical findings to the PET pattern can help define which process s involved, which has prognostic implications the patient might find useful. SPECT evaluation with ^{131}I MIBG is another technique which is available and might be of benefit in such subjects.

It should be recognized that diagnostic accuracy of those tests remains observer-dependent, and that a decision as to whether they might be indicated will rest, in addition to the parameters discussed above on the confidence the clinician will have in the quality of reporting offered. Issues such as experience of the reader, and the use of computer-assisted interpretation software, should be discussed between the clinician requesting the study and the imaging specialist reporting it.

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