Imaging of Brain Perfusion

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Introduction

Brain perfusion by SPECT or PET is a well-established and reliable method to measure regional cerebral blood flow (rCBF). The normal adult brain perfusion is symmetrical with higher tracer distribution in the temporal, parietal and occipital (visual) cortices, basal ganglia, thalami and cingulate gyrus than in the white matter and interhemispheric fissure [1]. Depending whether the eyes are open or closed, an increase of ca. 30 % more in the occipital visual cortex can be observed [1]. Motor and sensory stimuli can have asymmetrical effects. In the newborn, perfusion is slightly lowered in the frontal and temporoparietal regions and reaches an "adult" pattern within the first 2 years of life [1]. As the same SPECT pattern may be encountered in several pathologies (Table 1), detailed knowledge of the patient's symptoms and the functional area of the brain likely to be involved is important.

Indications

The human brain has about 130 billion neurons and weights only 2 % of a human body mass, albeit it consumes 20 % of the total body's oxygen supply [2]. The most common indications for rCBF by SPECT and PET are summarized in Table 2, and the following sections will detail these different clinical indications. SPECT is more available and less expensive as PET, but it has a larger radiation burden (Table 2) [3].

Dementia

Both SPECT cerebral perfusion imaging and PET glucose metabolism imaging have been widely used over the last decades to help in the diagnosis of Alzheimer (AD) and Lewy body (DLB) dementias. The main difference with PET using ^{18}F-fluorodeoxyglucose is a better spatial resolution as compared to SPECT. As cerebral glucose metabolism is coupled to neuronal function as the main substrate for energy production, any regional impairment in neuronal function is translated into a reduction of regional glucose metabolism and thus to rCBF [4]. A direct comparison study between ^{99m}Tc-HMPAO SPECT and ^{18}F-FDG PET was performed in 98 patients ($n=38$ AD, $n=30$ DLB, $n=30$ controls) [5]. Visual cues were decreased uptake in the precuneus and lateral parietal lobes in AD and DLB, a relative preservation of the posterior cingulate cortex in DLB, with more occipital loss in DLB, with reduced temporal and frontal uptake more likely in AD. The results showed the superiority of PET over SPECT for the diagnosis of dementia vs. no dementia (area under the curve AUC = 0.93 vs. 0.72, $P=0.001$) as well as for the diagnosis of AD vs. DLB (AUC = 0.80 vs. 0.58, $P=0.005$). Similarly, sensitivity and specificity were significantly better for PET than SPECT (85 and 90 % vs. 71 and 70 %, respectively). Thus, the authors recommended using ^{18}F-FDG PET rather than cerebral perfusion

Table 1 Perfusion pattern and brain disease

Cerebral perfusion pattern	Possible disease
Temporoparietal hypoperfusion	Alzheimer disease dementia
	Parkinson-related dementia
	Lewy body disease
	Normopressure hydrocephalus
Frontal/frontotemporal hypoperfusion	Pick's disease
	Frontotemporal degeneration
	Pseudodepressive dementia
	Progressive supranuclear palsy
	Chronic alcoholism
	Chronic schizophrenia
Multiple distributed defects	AIDS-related dementia
	Creutzfeldt–Jakob disease
	Vascular dementia

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Table 2 Indication to cerebral perfusion imaging with SPECT or PET

Cerebral perfusion imaging	Clinics	Research
Epilepsy	SPECT, PET	SPECT, PET
Traumatic brain injury	(SPECT)	SPECT, PET
Cerebrovascular disease, Moyamoya disease	SPECT, PET	SPECT, PET
Brain infection, brain inflammation	(SPECT)	SPECT, PET
Dementia	(SPECT)	SPECT, PET
Psychiatric disorder	(SPECT)	SPECT, PET

Rare indications are in parenthesis
Note: Radiation dose SPECT 4.3–8.5 mSv (ECD) or 5.1–10.2 mSv (HMPAO); PET 0.5–2 mSv

SPECT for the differential diagnosis of dementia, if functional imaging is indicated. They recommend adapting national and international guidelines based on these results.

Also, the role of structural and functional imaging techniques for the common dementias (AD, DLB, vascular dementia and frontotemporal lobar degeneration) is changing over time [6]. Anatomical imaging of hippocampal volume loss is not specific to mild cognitive impairment and AD and also present in depression, post-traumatic stress disorder and alcoholism, explaining why functional imaging has better sensitivity and specificity [7].

Traumatic Brain Injury (TBI)

Lesions detected within 72 h of a TBI using SPECT were 40 % more numerous than detected by CT scan and even in regions not detected by MRI; these abnormalities observed up to 1–6 months after the injury [8]. SPECT is a powerful tool for TBI research in the field of cerebrovascular disease and cognitive disorder and can be useful in evaluating patients with neurological and psychiatric sequelae after TBI [8]. SPECT imaging has the potential for estimating rCBF in the acute phase of TBI, but routine clinical implementation is lacking, however. With the newest quantitative SPECT/CT, it has the potential to quantify CBF in absolute value.

TBI imaging with PEt allows detecting regional brain ischaemia [8], and increased ischaemic volume has been shown to correlate with poor outcome. PET logistics for CBF imaging is complex and costly; it is therefore only available in few TBI centres worldwide. However, SPECT and PET suffer from the absence of bedside imaging directly in the neurointensive care unit, and small, xenon CT scanners emerge as an economical imaging technique that can be used directly at the bedside. Also, novel, bedside SPECT and PET scanners are in development and could also be a major game changer in the future.

Trauma impairs neuronal activity and interrupts connections with other brain or cerebellar regions, which become hypoperfused on SPECT at a distance from the injury site. This deafferentiation or diaschisis provides insight into the pathophysiology of the symptoms [9]. However, the most commonly seen corticocerebellar diaschisis has usually no relevance in clinical practice [9].

A special form is the dementia provoked by chronic traumatic head injury (*dementia pugilistica*) [7]. Functional imaging of retired American football players has found diffuse cortical hypoperfusion with extensive involvement of frontal and anterior temporal lobes [7]. It would be expected that amyloid imaging would be negative, as it is uninvolved in chronic traumatic encephalopathy.

Cerebrovascular Disease

Vascular Dementia (VaD) It originates from a multivessel disease (multiple microvascular infarcts) or ischaemic brain injury (sudden onset after initial stroke) [7]. Thus, functional brain imaging of VaD presents diverse patterns ranging from a single large stroke to multiple, small focal defects [7]. To complicate the situation, AD and VaD frequently coexist. There is also more frequently diffuse focal defects seen anteriorly, but this is no way an absolute criterion [7].

Although MRI is the method of choice for investigating VaD, it does not provide useful functional information [10]. SPECT brain perfusion with acetazolamide challenge provides a possible measurement of cerebral hemodynamic reserve for investigating VaD [10]. This underused application could benefit from standardization and long-term follow-up studies [10]. Indeed, SPECT brain perfusion baseline and/or with pharmacological acetazolamide test might have a role in screening, diagnosis and monitoring of patients with VaD [10]. As baseline cerebral SPECT measures rCBF, which reflects the neuronal activity, it would allow earlier detection of functional abnormalities, which precedes clinical symptoms of dementia; SPECT would thus be independent of cognitive reserve allowing highly functional individuals to still perform well on psychometric testing. The acetazolamide test was developed to assess cerebrovascular reserve in relation to chronic cerebrovascular diseases. It tests the ability for the brain vasculature to regulate and maintain adequate rCBF by decreasing

vascular resistance in the presence of chronic vascular disease. Acetazolamide enters the blood–brain barrier and induces increase in rCBF due to carbonic anhydrase blockade leading to acidosis, a very potent stimulus of rCBF. Using same-day, dual studies of baseline rCBF and acetazolamide-induced increase in rCBF, quantitative analysis allows identifying small abnormalities in vasodilation. This cerebrovascular reserve might represent the stroke risk predicting future cognitive complications [10]. Thus, vascular cognitive impairment (VCI) contains large-vessel post-stroke dementia, small-vessel subcortical dementia and brain chronic hypoperfusion [11]. In clinical practice, SPECT might be indicated in subcortical ischaemic vascular dementia for the diagnosis of vascular-associated component (differential diagnosis of frontotemporal dementia [hypoperfusion of frontal and anterior parts of the temporal cortices] vs. subcortical frontal syndromes [slight hypoperfusion of the medial prefrontal and anterior cingulate cortices]) allowing to better manage frontal subcortical syndromes with anticholinesterases [10]. Several studies indicate that vascular pathology affects cerebrovascular reactivity and cerebral metabolism finally leading to cognitive dysfunction, while no link is apparent between microangiopathy on MRI (white matter hyperintensities) and cognitive impairment [10]. SPECT-measured diminution in cerebrovascular reserve identifies the cerebral area of increased risk of stroke as demonstrated in patients with carotid occlusive disease or other diseases such as arterial hypertension, orthostatic hypotension, cardiac failure and dysautonomia [10]. Prevention of vascular episode/stroke by preventive medical therapy of cardiovascular risk factors seems to be the most effective, as well as efficient surgical approaches (carotid stenosis) and anticoagulation (in atrial fibrillation). Waiting for larger studies demonstrating a clear link between cerebral hypoperfusion and cognitive decline, from which a screening strategy would emerge, Farid et al. [10] recommend SPECT brain perfusion imaging in patients with: (i) severe or uncontrolled hypertension and (ii) multiple cardiovascular risk factors and already demonstrated cardiovascular impaction of target organs such as retinopathy or kidney failure. A stricter control of risk factor could then present or slow the evolution from predementia to manifest dementia in these populations.

Arterial Occlusion Patients with aneurysm of the internal carotid may not be suited for surgery and would undergo a balloon occlusion of the artery, in which effect on cerebral blood flow can be demonstrated by brain perfusion SPECT with an injection performed at the 15th min of a 20-min balloon occlusion test [1]. Focal or diffuse hypoperfusion can be seen, and the location and severity of the defects are important in deciding if carotid occlusion can be permanent or a different approach has to be used [1]. An illustrative example is given in Fig. 1.

Identification of Ischaemic Penumbra Cerebral perfusion by PET is the only imaging tool that can identify the presence of ischaemic penumbra (threshold for infarction and irreversible damage) by measuring rCBF, regional metabolic rate for oxygen and the regional oxygen extraction fraction, from which critically perfused but potentially salvageable tissue can be identified [2]. However, the complex logistics and the need for cyclotron-produced O^{15} have kept this modality to a research tool never applicable to clinical routine.

Normal global rCBF is about 45–55 mL/100 g/min (grey matter 80 and white matter 20 mL/100 g/min), and flow is altered by cerebral pulse pressure (50–150 mmHg). The functional threshold for developing paralysis and abolishing the electrocorticogram evoked potential varies from 6 to 22 mL/100 g/min [2]. In PET studies, which are considered as the golden standard for penumbra [12], three regions can be defined after an ischaemic insult: (i) the core of ischaemia transiting to necrosis for rCBF <12 mL/100 g/min; (ii) the penumbra region with flows between 12 and 22 mL/100 g/min, which is still a viable tissue with uncertain chances for infarction or recovery; and (iii) hypoperfused area >22 mL/100 g/min not primarily damaged by lack of blood supply [2]. SPECT equivalent to define penumbra has been defined as 20 % of the activity of the contralateral normal region (corresponding to 20 mL/100 g/min).

As recombinant tissue plasminogen activator (tPA) must be given intravenously within the first 3 h of stroke onset, there is insufficient time to perform SPECT or PET before tPA therapy [12]. However, a patient with stroke more than several hours or in unknown time of onset ("awakening stroke") and those with progressive stroke may be still beneficial in patients not suited for CT or MR imaging [12].

Moyamoya Disease This chronic stenooclusive vasculopathy (also called idiopathic intracranial angiopathy) affects the terminal internal carotid arteries and has been first described in 1969 [13]. Its origin remains unknown, and clinical manifestations are ischaemic stokes and transient ischaemic attack, with a propensity for the fragile collateral network to bleed resulting in haemorrhagic strokes [13]. The measure of the cerebrovascular reserve CVR using a vasodilator (hypercapnia or acetazolamide) is informative in moyamoya disease. Decrease rCBF or increased regional oxygen extraction fraction (rOEF) by PET or decrease of CVR by SPECT may indicate impending ischaemia [13]. These can aid in choosing treatment options, monitoring the disease and evaluating the effect of revascularization surgery [13, 14].

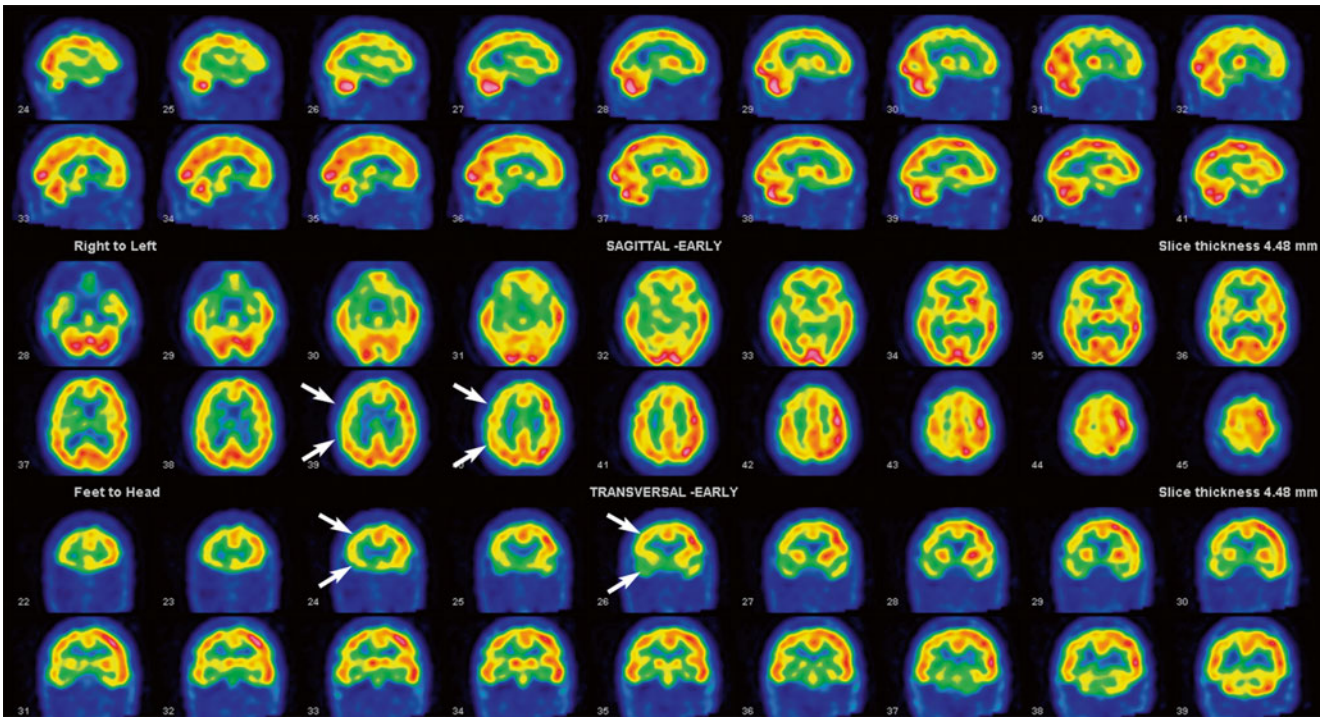

Fig. 1 Case of a 64-year-old woman with a partial thrombosis of the right internal carotid at the origin of the posterior communicant artery. The patient underwent a 37-min balloon-induced right carotid occlusion. The ^{99m}Tc-ECD was injected 5 min before the end of the occlusion, and SPECT imaging study was performed. The sagittal, transversal and coronal slices show an asymmetry in disfavour of the right side (*arrow*) including decreased striatum uptake

Epilepsy

Brain SPECT can localize the origin of the seizures for surgical therapy, especially in temporal epilepsy, which can be cured surgically in more than 70 % of the patients (as compared to extratemporal epilepsy where only 40–50 % have surgically addressable seizures) [1]. SPECT studies are performed ictally (sensibility 97 %, specificity 100 % in temporal lobe epilepsy, with a radiopharmaceutical injection typically within 5–10 s of the seizure onset) under EEG monitoring and interictally, i.e. >24-h seizure-free (sensibility 97 %, specificity 100 %) [1].

The accuracy of ictal SPECT can be enhanced by comparing it to interictal state using co-registration, automated subtraction techniques as "subtraction ictal SPECT co-registered to MRI" (or SISCOM) routinely available (Fig. 2) [15], as well as statistical parametric mapping (SPM) [16]. The SISCOM analysis can be falsely negative due to subclinical seizure activity at the time of injection in the so-called interictal scan [15]. This can be avoided if EEG is always performed during the injection. Concerning the injection, one has to consider that the radiotracer take 15–20 s to reach the brain, so that "ictal" SPECT is actually already showing the start of seizure propagation, which can affect also a different lobe (contra- or ipsilateral), with different patterns that have been described in the literature [15]. What is important is to know that injection delay of less than 20 s after seizure debut is significantly correlated with correct localization and that the largest and most intense cluster is likely to represent the seizure onset [15]. If injection occurs in the immediate post-ictal phase, a post-ictal switch can be observed about 60 s after seizure termination, where the area becomes hypoperfused with poor localizing accuracy due to similar changes in multiple brain regions [15]. Techniques for imaging specific receptor systems with SPECT or PET are in development and likely have increasing importance in better understanding the mechanism of seizure and epilepsy [15]. Usually, brain SPECT imaging of epilepsy requires a specialized team and clinical setting, not only with a dedicated nuclear medicine physician experienced in ictal SPECT and interictal ^{18}F-FDG PET, but also a neurologist specialized in epilepsy, a neurosurgeon, an electrophysiologist, a neuroradiologist, a psychologist and psychiatrist and nurses trained in administering radiopharmaceuticals [16].

PET is being used in epilepsy, but with a different tracer—^{18}F-fluorodeoxyglucose—which is not a perfusion tracer. Traditionally, interictal PET shows hypometabolism in the seizure focus [17]. Interestingly, ictal PET is possible in focal status epilepticus and has proven to be useful [18].

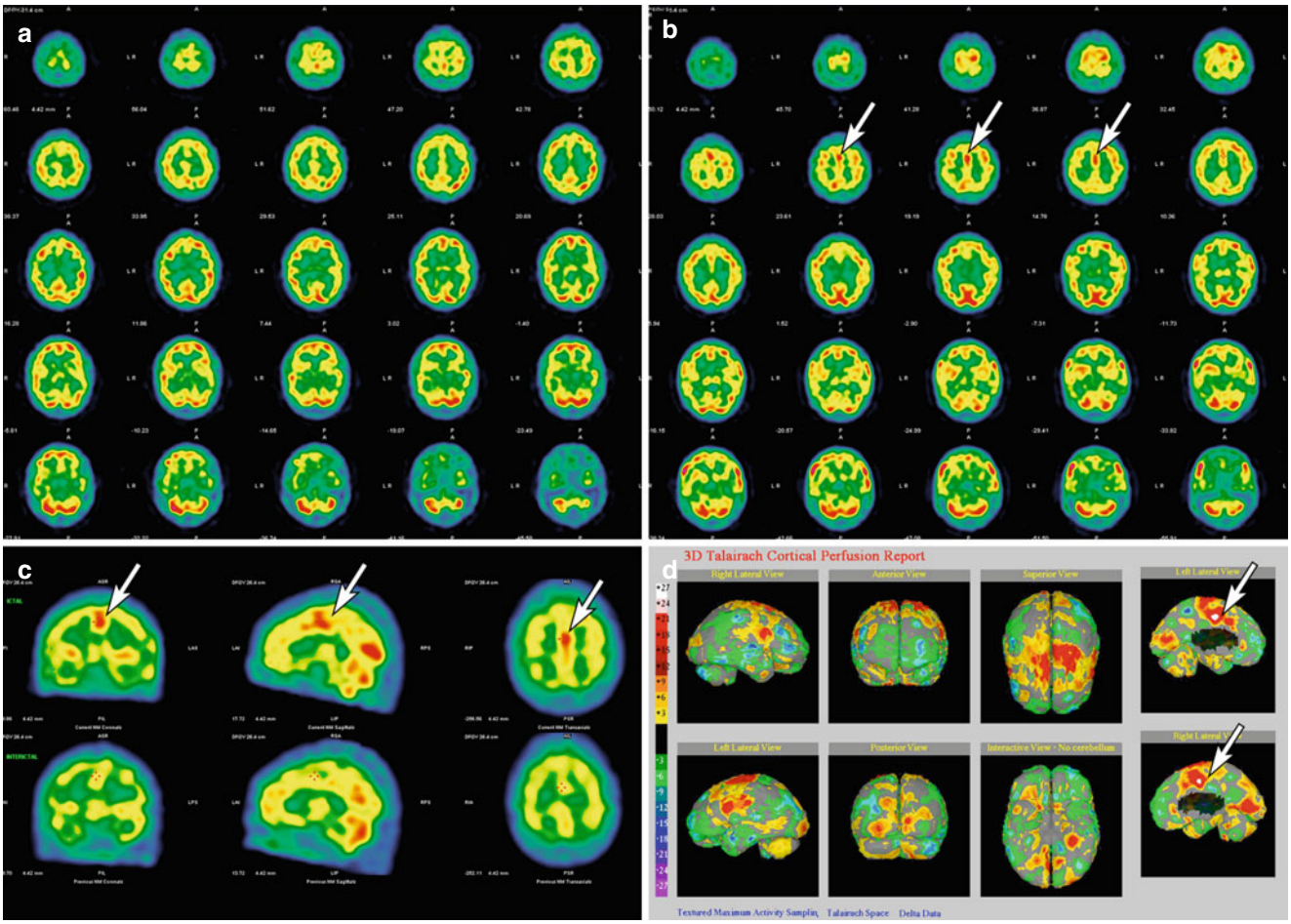

Fig. 2 Case of a 31-year-old man with pharmacoresistant epilepsy with 5–10 seizures per night and up to 4 diurnal seizures. The patient was hospitalized for an interictal (**a**) and ictal (**b**) SPECT rCBF imaging study using ^{99m}Tc-HMPAO. The comparison of both studies revealed a small focal precentral lesion (*arrow*) in the midline (**c**) which lateralization was difficult to precise. The SISCOM analysis (**d**) is also clearly pinpointing the midline cortical precentral localization of the seizure origin. Surgery was performed after electrocorticography and showed type-Ia frontal cortical dysplasia. Since then, the frequency of the seizure greatly regressed (focal seizure 1 every 4 days)

Brain Infection

In HIV encephalopathy, rCBF shows decreases cortical uptake due to microvascular changes in a "moth-eaten" appearance with multifocal defects in the basal ganglia with a decreased white matter rCBF [19]. The pathophysiology might be due to cytokines and macrophages and is correlated to the number of cotton-wool spots [19]. Thus, SPECT may be useful in the presence of psychosis or mild attentional impairment or depression in the presence of normal CT or MRI [19]. This pattern is not specific to HIV encephalopathy and can be observed in chronic cocaine users, chronic fatigue syndrome patients or mild trauma [19].

In brain herpes simplex encephalitis, SPECT rCBF changes with increased temporal lobe activity may be present in the early stage where MR, CT and cerebrospinal fluid might still be negative [19].

Brain Tumors

Cerebral blood flow by $H_2{}^{15}O$-PET has been found to be decreased in adult glioma, with most malignant glioma having the deepest rCBF reduction [16]. There is no correlation between $H_2{}^{15}O$-PET with the glioma grade of brain tumour [16].

Major Psychiatric Disorder

SPECT and PET have been used as a research tool in many studies [1, 20]. However, they are not routinely used in psychiatry and have the potential for individualizing treatment, monitoring response and modifying treatment when warranted. The rest of this section will present evidences for such a use in psychiatry, for a number of major diseases:

- *Attention deficit hyperactivity disorder* (*ADHD*) – Several studies investigated rCBF changes in ADHD, to show decrease in brain perfusion in premotor cortex and prefrontal cortex and hypoperfusion of striatal and periventricular structures [20]. Response to methylphenidate therapy has been investigated and shows prefrontal rCBF normalization, while in one study nonresponders may have increased activity in the anterior cingulate at the baseline [21].
- *Obsessive-compulsive disorders* (*OCD*) – The anterior cingulate cortex is thought to be important in the pathogenesis of OCD [20], and SPECT may identify patients benefiting from anterior cingulotomy for symptom relief in one study [21].
- *Gilles de la Tourette's syndrome* – In this rare, severe tic syndrome, closely related to obsessive-compulsive disorder, hypoperfusion of the frontal lobes, cingulate gyrus and basal ganglia/thalami may be found [1].
- *Schizophrenia* – In schizophrenia (1 % of the population), SPECT-derived rCBF generally shows frontal hypoactivity (especially during a specific task), and perfusion changes in the basal ganglia (eventually due to neuroleptic drugs) and temporal lobes hypoactivity (usually left-sided) frequently associated with ipsilateral frontal hypoperfusion have been observed [20]. Patients that are medication-free may usually present with frontal hyperperfusion and depending on the presence of positive symptoms (auditory, tactile, visual or olfactory hallucination, etc.) present increased precuneus activity or frontal and temporal hypoperfusions if negative symptoms are present (poor eye contact, speech or hygiene, apathy, etc.) [20]. If radiopharmaceutical injection occurs at the time of visual or auditory hallucination, hyperactivity in the associated visual or auditory cortex is observed. With treatment, rCBF improvements in frontal, temporal and basal ganglia, as well as motor cortex, are observed. In chronic or progressive disease, significant hypoactivity has been observed in the inferior parietal cortex, cuneus and posterior temporal lobe [22].
- *Anxiety and depression* – These two illnesses are extremely common nowadays and present a major healthcare problem incurring significant societal losses. Affected people seek actively out a cure, and involved medications can make additional harm due to side effects. SPECT-measured rCBF in medication-free patients shows hypoperfusions in the prefrontal, limbic, paralimbic regions, cingulate gyrus and left caudate nucleus [20]. In both unipolar and bipolar depression, hypoperfusions are seen in prefrontal, limbic and paralimbic regions, and lateral frontal hypoperfusion is involved in the acute depression in the elderly [20]. Increased activity can be seen in the basal ganglia and frontal lobe of the patient with anxiety. Frequently, anxiety and depression coexist. The severity of depression is correlated to hypoperfusion in the left cingulate cortex, lentiform nucleus and parahippocampal gyrus and increase in right posterolateral cortex [20].
- *Substance abuse and addiction* – Disseminated alterations of rCBF can be observed in short- and long-term substance abuse and dependence. Disappearance/improvements after abstinence have been observed in alcohol, cocaine, crack and heroin [20], suggesting that arterial spasms may cause the observed defects. Patients with history of inhalation of industrial solvents (paint, glue, gasoline) present similar perfusion abnormalities [23].
- *Autism* – This early and severe developmental disorder (20–50/100,000 births, M:W = 1.5:1) may induce decreased temporal lobe perfusion, although many cerebral SPECT are normal and each individual might have his unique perfusion pattern. Up to 30 % of autistic children may develop epilepsy [20].
- *Panic disorder* – Decreased rCBF is seen in the frontal lobes of patients with this disorder during a yohimbine challenge, while healthy volunteers did not show this decrease [1, 24].

Clinical Use of Brain SPECT in Psychiatric Diseases The exact use of rCBF for tailoring patient therapy in the clinics is still under investigation, but studies have shown potential use depending on the gross rCBF changes (a more detailed review and references are available in [20]):

- *Frontal hyperactivity*: It predicts a positive response to serotonergic medication in depression and OCD, as well as a response to cingulotomy in OCD or to sleep deprivation or repetitive transcranial magnetic stimulation in depression. It helps also to distinguish OCD from ADHD.
- *Prefrontal hypoperfusion*: It is associated with a negative response to serotoninergic medication in depression and clozapine in schizophrenia. It also predicts relapse in alcoholism and improved response to acetylcholinesterase inhibitors for memory and behaviour in Alzheimer disease. It also predicts poor ketamine response in fibromyalgia and improved response to stimulants in ADHD patients during concentration challenge.
- This pattern is associated with antisocial and impulsive behaviour and murder, as well as chances of completed suicide. When this pattern is observed in depressed patients, the physician should be more vigilant in their care and seek family support, as patients are less likely to respond to typical medication.
- *Temporal lobe abnormalities* (*hyper-/hypoperfusion*): When present in patients with mood instability or temper problems, it provides a rational for anticonvulsants

therapy. In the presence of memory or learning issues and a hypoperfusion pattern, it may show the usefulness of introducing acetylcholine esterase inhibitors.

Although SPECT has been used as a tool for research for in vivo probing of the brain function, it is not used in daily practice of psychiatry. SPECT may have the potential for personalizing treatment based on each patient's brain pathophysiology, but its true value and cost-efficiency need to be evaluated further. Currently, fMRI has superseded SPECT and PET for the real-time evaluation on the effects of drugs on cognition and impulse behaviour because of a better temporal resolution [3]. The true strength of PET and SPECT in psychiatry lies in the emergence of novel radiopharmaceuticals targeting specific receptor systems [3].

Technical Considerations

The current procedure guidelines European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) were published in 2009 [25, 26]. Relevant history including past drug use or head trauma and results of neurological, psychiatric, mini-mental status or neuropsychological testing [26].

Patient Preparation

The patients should be instructed to avoid substances known to affect CBF (alcohol, caffeine, energy drinks and any drugs know to affect CBF) the day of the examination. The injection of the radiopharmaceutical should be done after a 20-min resting period in a quiet, dark (or dimly lit) room without moving, to avoid any neurological stimulation. Ideally, the same room and preparation should be used uniformly at a given centre.

If sedation is needed for the images, the radiopharmaceutical administration should precede the sedation, as to avoid blood flow changes related to sedation.

Radiopharmaceuticals

Basically two tracers are used for brain perfusion SPECT: ^{99m}Tc-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO, Ceretec™) and ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD, Neurolite™) [25, 26]. ^{99m}Tc-HMPAO requires freshly eluted (<2-h old) ^{99m}Tc solution and is less stable in vitro than ^{99m}Tc-ECD, which has a higher grey-matter-to-white contrast contributing to higher image quality. Both tracers present an uptake which is not entirely proportional to rCBF with underestimation of higher blood flows and overestimation at lower blood flows [27, 28]. They enter the brain cells because of their lipophilicity and undergo a lipophilic-to-hydrophilic conversion, which allows them to be trapped within neuronal and glial cells during its first passage and occur within 1 min of tracer injection. There is a small difference between tracers, as ^{99m}Tc-HMPAO reflects blood flow arrival to cerebral regions, while ^{99m}Tc-ECD would measure a more perfusion–metabolic uptake, because of a de-esterification needed for cellular trapping [29]. The more rapid urinary excretion of ECD favours its dosimetry, with about 4–8 mSv (ECD) or 5–10 mSv (HMPAO).

Quality control should be performed according to the manufacturer's instruction, and purity should be >90 % (ECD) and >80 % (HMPAO). After reconstitution, one should respect the delay for stability (HMPAO: 4 h, ECD 6 h) [25]. The activity is 555–1100 MBq (typically 740 MBq) in either radiopharmaceutical; in children, use the EANM dosage card (version 1.2.2014) with the weight-based multiplication with the baseline activity (ECD: 32.0 MBq; HMPAO: 51.8 MBq) with a minimum activity of 110 MBq (ECD) or 100 MBq (HMPAO) [30].

Of note, ECD is not commercially available since summer 2011 due to production. However, a new FDA-approved manufacturing site has been approved for commercial use in early 2015.

For brain perfusion imaging with PET, the short-lived (2-min half-life), cyclotron-produced ^{15}O-positron-emitting radionuclide is incorporated into chemical compounds (carbon monoxide $C^{15}O$, carbon dioxide $C^{15}O_2$, and water $H_2{}^{15}O$) or as a molecular tracer ($^{15}O_2$) and given intravenously or inhaled and is distributed according to physiology, allowing to mathematically quantify CBF, cerebral blood volume (CBV), the oxygen extraction fraction (OEF) and the cerebral metabolic rate of oxygen ($CMRO_2$). The advantage of PET over SPECT is clearly the absolute quantification, but a major drawback is the costly infrastructure and logistics for obtaining the short-lived radioisotope.

Acquisition Protocols

The best image resolution is reached with fan-beam collimators, and CT-based attenuation correction allows improving image quality and anatomical correlation. The ideal SPECT camera is a high-resolution dedicated camera but, alternatively, is a general-purpose camera with fan-beam collimators or high-resolution, parallel collimators; the SPECT camera must follow appropriate quality control programme [9]. Usually at least a 128×128 matrix size is chosen with a pixel size at least half of the camera's FWHM resolution. The acquisition duration should maximize total image count while minimizing patient motion, and the number of projections should be kept close to the number of pixels in the

matrix (e.g. 128 × 128 matrix leads to 3° projections for 360° or 120 projections); higher projection number brings minimal reconstruction benefits, and too low projection number will cause reconstruction artefacts [9]. Total acquisition time should be close to 20–25 min (triple-head camera) or 30 min (dual-head camera) [25].

Attenuation correction should be applied in all cases (Chang method or dedicated CT acquisition in SPECT/CT system) during reconstruction [25]. The number of image counts (ideally >5 million) should guide the filter to be used, with the higher the number of counts, the sharper the filter [9]. Scatter correction should be applied for better signal/noise ratio and lesion detection accuracy [25].

PET may be routinely done in large centres, but it might be more difficult to organize in an emergency setting. Usually CBF, OEF and $CMRO_2$ are measured using ^{15}O-labelled compounds [31].

Pharmacological Interventions

Acetazolamide challenge test—Intravenous injection of acetazolamide (Diamox™, adults 1 g; children 14 mg/kg) induces a vasodilation and increases rCBF by 30–50 % above baseline in 20–30 min, which returns to normal within 2–3 h [1]. Areas with low perfusion will see little changes to the challenge. Side effects include mild vertigo, tinnitus, paresthesia and nausea, and contraindications are allergy to sulfa, skin rash, bronchospasm, anaphylactoid reaction or <3 days after acute stroke or intracranial haemorrhage, as well as sickle cell patient at risk of veno-occlusive crisis) [25]. One-day protocol can be performed with split dose (1st dose = $^1/_3$ of activity, 2nd dose = $^2/_3$ of the total activity) which allows to perform baseline and challenge acquisition [25].

Alternatively, hypercapnia (inhalation of 5 % CO_2), dipyridamole or adenosine can be used and induces the same increase in rCBF [19].

Processing

Slice orientation is also important, and several reference systems are used (fronto-occipital plane similar to canthomeatal line in CT, fronto-cerebellar plane or temporal slices parallel to the longitudinal edge of the temporal lobe, useful for differentiating the mesial and temporal aspects of the temporal lobe for epilepsy or early Alzheimer-type dementia) [9]. The choice of the colour or black-and-white lookup table is arbitrary, but discontinuous scale may overestimate defects or asymmetry, and consistent normalization (e.g. to maximum count in the oblique slices) should be applied to avoid subjective image manipulations [9]. Iterative reconstruction including ordered-subset expectation maximization (OSEM) is available and can improve lesion detectability [25].

Usually images are interpreted visually using standard axial, coronal and sagittal plane [1]. Control groups using a minimum of 30 healthy volunteers can be used to define mean and SD in a semiquantitative approach usually using the cerebellum as a reference (or the pons in presence of cerebellar disease). Prior written patient information and consent is advised for provocation tests [9].

Major vendors have dedicated brain perfusion application to assess and display rCBF for each brain structural region (Fig. 3), with possibility to compare with normal population databases through statistical parameter mapping, and even some are freely available to academic institutions (Neurostat—Neurological Statistical Image Analysis Software, Department of Radiology, University of Washington, Seattle, WA, USA, http://128.208.140.75/~Download/), which runs mostly on older platforms using a DOS-like, cumbersome command language.

With the latest quantitative SPECT/CT scanners (e.g. Intevo xSPECT QUANT, Siemens), absolute quantitation can be obtained for SPECT ^{99m}Tc-tracers in Bq/mL with an accuracy of ±10 %. This may allow measuring absolute rCBF, but no comparison studies have been performed so far. Taking into account the difference in price between PET and SPECT and the fact that SPECT/CT may provide a cost-effective strategy for early identification and monitoring of the AD epidemics, such quantitative research should be encouraged [7].

Interpretation

Usually, brain SPECT interpretation is done stepwise [9]. First read sets of axial (or oblique temporo-occipital slices) and look for basic SPECT patterns, while the other sagittal and coronal slices will be used for confirmation or for additional findings. Identify then cerebral structures within the resolution of the images to identify lobes (eventually use an atlas as a guide). Using a standard regional order, visualize all cerebral regions (e.g. cortical regions in the caudal-to-cranial direction, cerebellum, temporal lobes, frontal lobes, occipital lobes and parietal lobes; mesial and lateral aspects of the brain being evaluated separately, as well as the subcortical regions [striatum, thalami, and white matter] and the pons). Then, global and regional tracer uptake is assessed for abnormalities (check for asymmetry, with attention to pattern due to incorrect tilts, which are easily identified on consecutives slices). Compare SPECT images to morphology (CT or MRI) (Fig. 3), as it is difficult to identify difference in uptake between periventricular white matter and lateral ventricles on SPECT only (e.g. hydrocephalus). When cerebral atrophy is present, partial volume effect may decrease brain uptake in the presence of cerebrospinal fluid within the cerebral cortex atrophy. Thus,

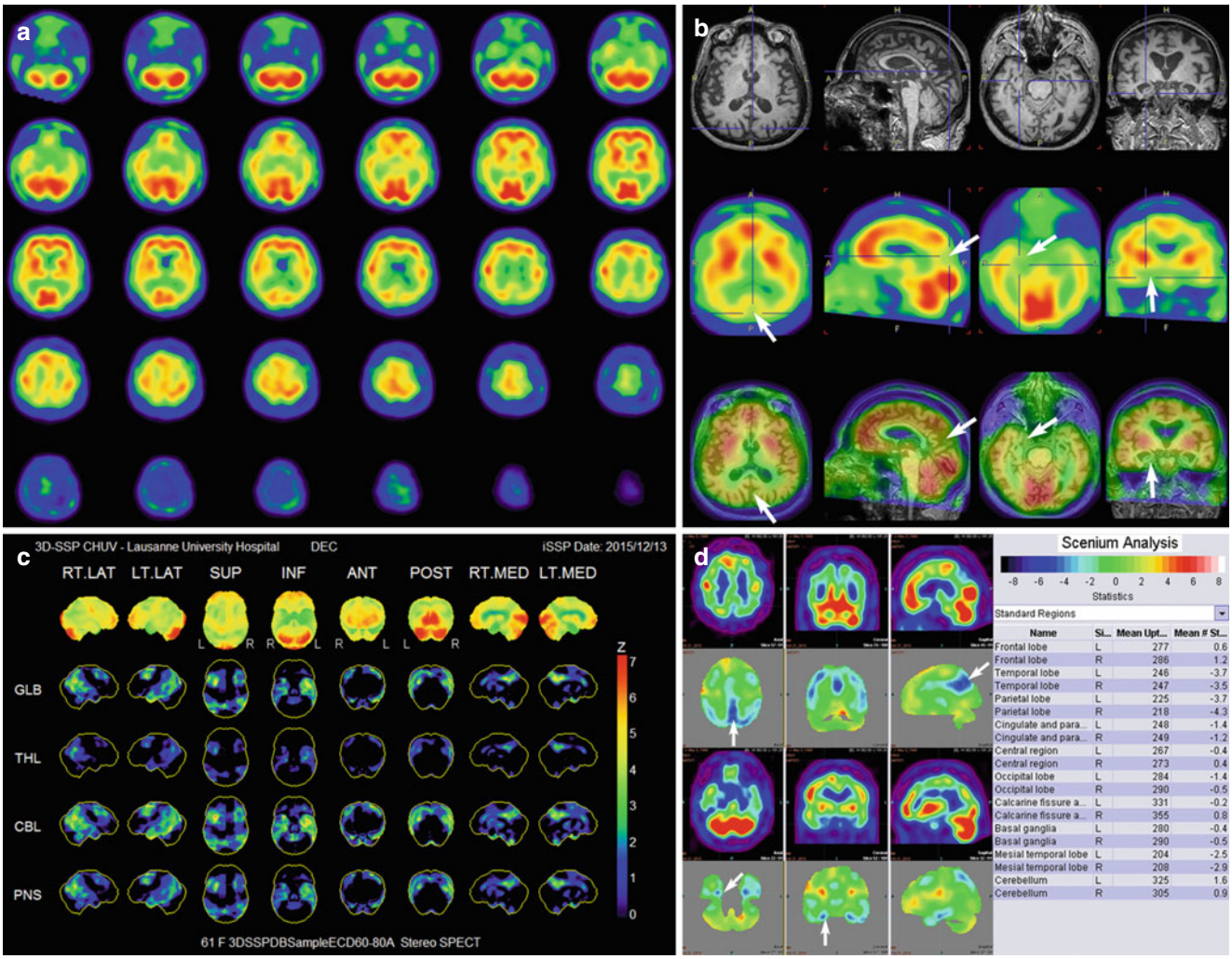

Fig. 3 Case of a 61-year-old woman with memory problems, aggressive behaviour, visual hallucination and agitation, with progressive degradation of symptoms over the last 2 years. The ^{99m}Tc-ECD SPECT (**a**) shows an important decrease of perfusion in the posterior cerebral cortex and temporoparietal cortex, as well as on the mesial side of the temporal lobe. These are accompanied of severe atrophy on the SPECT/MR fusion images (**b**, *arrows*). The comparison with databases of normal volunteers can be seen in (**c**) for *Neurostat* and (**d**) for the Siemens *Scenium* tools. The final diagnosis of posterior cortical atrophy (Benson-type) was retained, which is a rare form of neurodegenerative disorder mostly attributable to Alzheimer disease and characterized by visual deficits and atrophy of the parietal, occipital and occipitotemporal cortices)

indirect signs of cerebral atrophy should be searched for (enlarged interhemispheric fissure and marked separation of the basal ganglia), which should be confirmed by anatomical imaging. Advanced analysis software can correct for partial volume effect helping to define if hypoperfusion more marked than simply due to atrophy exists [9]. Finally distribution patterns should be recognized (hypoperfusion, absence of perfusion or hyperperfusion) taking into account the clinical context and morphology. Hypo- or hyperperfusion can be of vascular or axonal origin. Look for pattern distribution of abnormal perfusion such as vascular territories, diaschisis, dementia patterns, temporal lobe epilepsy or herpetic encephalitis. Such a systematic approach is valuable to define the possible aetiology to observed SPECT uptake.

Reporting

A concise report is appreciated by the referring physician, and the initial paragraph should include the requisite for the study, followed by a technical description of the study technical conditions, including the activity and nature of the radiopharmaceutical used and patient-centred conditions possibly influencing brain perfusion and eventually technical pitfalls important to understand the results and the interpretation [9]. The results should describe the localization and type of the abnormalities with description of the anatomical imaging comparison. The interpretation and conclusion should lead to a diagnosis likelihood if the requisite is about a specific clinical application (dementia, epilepsy,

carotid occlusion, etc.) When the role of brain perfusion has not been studied extensively, such as in behavioural disorders, prudence should be exerted.

Quality Control

Regular SPECT quality control should be run in accordance with the specific country's requirement [25].

Pitfalls

Technical pitfalls include unwanted patient movement or unintended cerebral activation, interaction with drugs acting on rCBF and inappropriate processing (background subtraction, thresholding, inappropriate patient database, discontinuous colour table with discrete scale, etc.) [25].

Sedating medication alters rCBF, and >5 min should be waited between the injection time and induction of the sedation, as not to alter image distribution [26]. Patient motion may degrade reconstruction and quality control on SPECT reprojections [26].

Breastfeeding should be interrupted for 24 h after injection of ^{99m}Tc compounds [25]. Sometimes, lack of cooperation or inability to stay still for 30 min limits the realization of the study; in such cases, conscious sedation with benzodiazepine can be used but it should be administered >5 min after tracer injection [26].

Conclusion

Brain perfusion using SPECT is a well-recognized clinical application routinely available in most nuclear medicine centres with applications in cerebrovascular disease, epilepsy and dementia, although this latter is gradually being replaced with PET. Anatomical correlation and close collaboration with the referring clinician enhances the clinical value of brain perfusion SPECT. Brain perfusion with SPECT and PET is still of great value and often unappreciated for imaging functional abnormalities that have not translated into anatomical abnormalities. Further work is also warranted to see the value of cerebral perfusion and cerebral perfusion reserve by SPECT for the evaluation of patients with cerebrovascular disease and risk factors to prevent or slow down the progression from predementia to dementia.

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