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EDITORIAL

The renaissance of functional ^{18}F-FDG PET brain activation imaging

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For a few years now, positron emission tomography (PET) has benefited from a renaissance of functional imaging through ^{18}F-FDG PET brain activation studies. The first PET studies involving activation brain imaging nevertheless emerged in the 1980s, using intravenously administered oxygen-15-labelled water (^{15}O-water) [1, 2]. This approach was used to measure regional cerebral blood flow (rCBF), and has been shown to be a sensitive method for quantifying regional brain activation during specific tasks [3, 4]. Such functional imaging studies proved extremely useful for mapping brain activation patterns involved in cognitive tasks such as word reading, mental imagery, timing or memory [5, 6]. The first clinical validations of quantitative analyses using Statistical Parametric Mapping (SPM, Wellcome Trust Centre for Neuroimaging, London, United Kingdom) were thus performed with PET imaging [7]. These PET imaging studies preceded the emergence of functional magnetic resonance imaging (fMRI) in the 1990s, which depicts the engagement of different brain regions within a distributed system through fluctuations of the blood-oxygen-level dependent (BOLD) signal [8]. fMRI applications have since been extended to reveal additional information about the degree to which components of large-scale neural systems are functionally coupled together to achieve specific tasks. This phenomenon underpins the study of functional connectivity, which is mathematically defined as the statistical association between two distinct time-series, i.e. the connectivity between brain regions that share functional properties. The fMRI approach enables the study of functional connectivity within single subjects or groups through serial imaging of the brain in the so-called resting state (i.e. without any specific stimulus or task) or in a condition of task-dependent activation [9].

In the past two decades MRI has largely supplanted PET for studies of brain activation, due to the lack of exposure to ionizing radiation and because of the superior spatial and especially temporal resolution, which allows for dynamic measurement of multiple responses within a single imaging session [8]. As such, fMRI has substantially advanced our understanding of normal and pathological brain functions, whether in resting-state or activation functional imaging studies [10, 11]. Nevertheless, fMRI does have some disadvantages. At the single-subject level, fMRI exhibits low signal-to-noise ratios and low variance concentrations in comparison with PET [12]. Indeed, to represent a given aggregate percentage of variance, many more components are needed for fMRI than for PET. Therefore, multiple runs of the same fMRI protocol are required to increase the sensitivity of measurements. Furthermore, recent work has shown that the signal-to-noise ratio may vary dramatically between fMRI runs, especially when performing a brief task, which degrades the robustness and reproducibility of this method at a single-subject level [13]. All these disadvantages generate poor out-of-sample replications in fMRI studies. In addition, fMRI is vulnerable to ferromagnetic artefacts, which are especially prominent in anterior and ventral brain areas [14]. These limitations could also cause others difficulties in performing such imaging due to the high prevalence of treatment with implantable devices for neurostimulation, most of which are not MR compatible [15]. Noise generated by the gradient coils, which could adversely affect listening to auditory inputs and can make recording of spoken outputs difficult, or movement artefacts that arise from speaking or other orofacial movements, could also cause others technical limitations [14]. Furthermore, the BOLD signal is a composite of effects attributable to the

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cerebral metabolic rates of oxygen, the cerebral blood flow, and the cerebral blood volume changes in response to excitatory neurotransmission [16]. In light of the above and given recent technological advances, functional PET imaging may be experiencing a renaissance.

Fluor-18-labelled fluorodeoxyglucose (^{18}F-FDG) is the most widely used PET radiotracer due to its ability to provide an indication of the rate of glucose utilization by neuronal tissue, namely, the cerebral metabolic rate of glucose (CMRGlc), which directly reflects neuronal and glial activity [17]. ^{18}F-FDG is currently the most accurate in vivo method for investigating regional human brain metabolism, and its clinical use can be regarded as being established for a number of diagnostic questions in neurology (dementia disorders, movements disorders, neuro-oncology) and psychiatry [18]. On the other hand, ^{18}F-FDG PET imaging keeps an important clinical interest in epilepsy, particularly at inter-ictal state [19]. Beyond ^{18}F-FDG-PET, brain activation studies are performed in the clinical setting with perfusion SPECT (single photon emission computed tomography) in ictal epilepsy [20]. An "ictal" scan, performed during an epileptic discharge, shows increased perfusion in the brain regions involved in seizure generation and early propagation [21]. Even though some activation studies have explored ictal ^{18}F-FDG PET [22], the temporal resolution of ^{18}F-FDG PET remains weak, having a longer uptake period (30 min) that leads to a mixture of interictal-, ictal-, and postictal-phase images [23], which renders the analysis of ^{18}F-FDG PET difficult. Until now, and with some rare exceptions (previously reported ictal epilepsy, neuro-oncology, autoimmune encephalitis [24]), it should nevertheless be noted that visual or quantitative analyses of ^{18}F-FDG imaging in a clinical routine typically rely on the identification of regions/voxels with relatively reduced metabolism. By contrast, functional ^{18}F-FDG PET brain activation imaging is based on the identification of relative increased metabolism.

Functional ^{18}F-FDG PET brain activation imaging may provide advantages to fMRI. Indeed, CMRGlc measured with ^{18}F-FDG PET is known to precede the relative transient decrease in BOLD signals without any magnetic limitations [25]. Thus, CMRGlc and BOLD signals provide distinct information due to the neurometabolic and neurovascular uncoupling [26]. Indeed, while the ^{18}F-FDG PET signal arises primarily from excitatory synaptic activity, which is localised to the grey matter tissue compartment, the BOLD-fMRI signal is more heavily weighted towards the draining veins and macrovessels [27]. In addition, better signal-to-noise ratios, variance concentrations and out-of-sample replications at the single-subject level are expected with PET imaging rather than fMRI [12], with unrivalled sensitivity in the ability to measure sub-picomolar concentrations [28]. Furthermore, activation ^{18}F-FDG PET imaging provides the unique opportunity to study functional imaging during interactions with different environments by timely dissociating radiopharmaceutical injection to acquisitions records. In these lines, activation PET studies have been performed to explore cerebral plasticity after walking [29] and cochlear implants benefits, which could bring about magnetic interference in fMRI during deafness rehabilitation [30]. In addition, a recent original study has been proposed to use PET imaging sensitized by virtual reality exposure to objectify a virtual reality exposure therapy (VRET) response in patients with acrophobia [31]. The principle is to immerse the patient in a computer-generated virtual environment [32], and in this case, VRET allows the patient to be virtually confronted with intense phobia cues. VRET is thus easily coupled with PET imaging in the activation state. This approach can be extended to other psychiatric diseases or other virtual environments. Interestingly, recent technologic and methodologic advances in PET have increased the development of functional ^{18}F-FDG PET brain activation imaging. The recent introduction of a solid-state digital photon counting PET detector, which enables faster time-of-flight timing resolution, allows for the realization of dynamic acquisitions with a high level of temporal resolution [33]. In parallel, original methodologic approaches have been developed, consisting of an analysis pipeline similar to that of fMRI, with a constant infusion of ^{18}F-FDG defining within-session differential metabolic responses [34–36]. This novel method of dynamic PET imaging, described as "functional PET" (fPET) imaging, offers high sensitivity and regional specificity for multimodal brain imaging for groups or at single-subject levels, with nevertheless the cost of an increase in ionization doses required to perform PET experiments. The slowly infusing ^{18}F-FDG over the course of the scan enables dynamic tracking of ^{18}F-FDG uptake. In a proof-of-concept study, this slow continuous infusion technique yields sufficient ^{18}F-FDG -PET signal in the occipital cortex during a checkerboard stimulation to be able to identify activation in the primary visual cortex [34]. Comparable results were recently obtained in the motor cortex [35, 36]. Interestingly, by using this novel method of dynamic PET imaging, the necessary task duration for reliable quantification of task-specific CMRGlu could be reduced to 2 minutes, therefore, approaching that of fMRI [36]. Looking further ahead, PET imaging with multiple ^{18}F-FDG bolus administrations may also be performed to further increase the temporal resolution of PET imaging.

As previously mentioned, fMRI has currently developed novel approaches for studying brain connectivity. Functional connectivity can be more specifically defined as the temporal correlation between spatially remote neurophysiological events, expressed as a deviation from the statistical independence across these events in distributed neuronal groups and areas. ^{18}F-FDG PET imaging interpretation has also recently evolved with the introduction of metabolic connectivity analyses, which refer to the relationships between the CMRGlc of different brain areas, in the same way as what is performed with the BOLD signal in fMRI [12]. Thus, metabolic connectivity at the group level can

be analysed in resting-state conditions with an inter-regional correlation analysis [37, 38] or with an independent component analysis or graph theory, which enables studying connectivity without any a priori hypotheses [39, 40]. Due to the increased temporal resolution of PET imaging systems, metabolic connectivity can also be studied in functional PET imaging at a single-subject level, using a constant radiotracer infusion as mentioned above, at rest or also using an activation task, enabling development of functional connectivity in PET. The increasing availability of the combined PET/MR system is a good opportunity to develop multimodal brain activation imaging [41, 42]. One study found a close association between local metabolic activity and functional connectivity [43], whereas another, using dynamic ^{18}F-FDG PET imaging, reflected differences in the temporal characteristics of glucose metabolism and brain activation as measured with fMRI [44]. In this line, the combination of functional and metabolic connectivity, named effective connectivity through the metabolic connectivity mapping, could help to study signalling hierarchies in the brain and their defects in brain disorders, such as hippocampal-cortical circuits in Alzheimer's disease or fronto-midbrain interactions in major depression [45]. In addition, it is well known that decreasing mean synaptic activity of a region, i.e., decreasing metabolic connectivity, reduces the region's sensitivity to afferent input from other regions, i.e., functional connectivity. Thus, the decoupling between both modalities could improve our understanding of the progressive evolution of neurodegenerative disorders [46].

Overall, recent advances in technologic and methodologic tools in brain PET imaging are conducive to a renaissance of functional ^{18}F-FDG PET brain activation imaging. Improved temporal resolutions in PET systems, development of metabolic connectivity at the group level and also more recently at the single-subject level, can allow ^{18}F-FDG PET imaging to be remade in the foreground of brain activation imaging. In this line, dynamic PET imaging, with a constant infusion of ^{18}F-FDG, defined as functional PET imaging (fPET), will enable the development of functional connectivity in PET. In addition, the multimodality approach, which integrates functional connectivity obtained with fMRI with the PET data, can also receive profound interest due to the potential complementarity offered by both modalities [47].

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Compliance with ethical standards

Conflict of interest None.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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