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Whole-body PET imaging: A catalyst for whole-person research?

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GRAPHICAL ABSTRACT

Whole-body (WB) and total-body (TB) PET imaging systems, in particular, can serve as exploration tools for the scientific community. They allow the study of inter-organ interactions with their unique ability to visualise multiple organs simultaneously operating at different time scales. (Figure created by Dall-e (Open-AI) and LKSS).

"You don't understand anything until you learn it more than one way."

Marvin Minsky (1927-2016)

Introduction

Living organisms maintain "homeostasis" through dynamic multi-organ systemic interactions (*1*). A considerable amount of energy is needed to fuel these interactions to promptly orchestrate multiple organs to respond to perturbations ("allostatic load") (*2*). For example, inflammation in response to infection or tissue damage is a critical survival mechanism to return to the original homeostatic state. In the case of ill-compensated systemic feedback loops ("allostatic overload"), persistent disruptions in baseline homeostasis may occur, which give rise to chronic diseases, such as arthritis, cancer, cardiovascular disease, or diabetes (*3*). These pathologies can, in theory, be characterised by deviations in parameters that describe a normative multi-organ network and that extend beyond their usual range.

Molecular imaging modalities, such as Positron Emission Tomography (PET), can provide valuable insights into the underlying homeostasis of living subjects using target-specific radiotracer imaging (*4*). Following its commercial inception, most of the clinical PET investigations focused on single-organ field-of-view (FOV) imaging (cardiology and neurology). With the introduction of a "whole-body" (WB) acquisition mode, that is the successive translation of the subject through the axial FOV of a PET system with slightly overlapping bed positions (*5*), the identification of hypermetabolic tumour lesions in oncology patients became the primary application of PET. Such a reductionist "lumpology" approach (*6*), however, caused a wealth of molecular information available from PET to be overlooked and discarded the concept of human physiology imaging.

The recent extension of the WB-PET concept to imaging extended axial imaging ranges with larger FOV systems, colloquially referred to as a total-body PET (TB-PET) has sparked interest in the PET

community to conduct multi-organ systemic investigations. TB-PET systems cover axial scan ranges of 1m (*7,8*) to 2m (*9*), which allows the synchronous measurement of signals from multiple organs. In addition, the richness of the multi-organ data derived from WB-PET notwithstanding (*10,11*), TB-PET is particularly unique as it satisfies two critical criteria for such causal investigations: the simultaneous acquisition of signals from multiple investigated distant organs and a high temporal resolution across the FOV (*12*). The combination of increased sensitivity and sub-second temporal sampling (*13*) provided by TB-PET could potentially aid in probing real-time multi-organ interactions (Fig. 1).

Multi-organ analysis with standard WB-PET

Traditional WB-PET with an axial FOV of ~20cm can already be used for multi-organ analysis. For example, simple inter-group comparisons of organ-based standardised uptake values (SUV) can provide crucial information regarding the underlying pathology. A recent study demonstrated that in a patient cohort with resected breast cancer, a high metabolic tumour volume and increased spleen glucose metabolism on baseline were associated with poor 5-y recurrence-free survival (*14*). The bespoke study hints toward a possible interaction between the tumour and the host immune system through the upregulation of hematopoiesis. Diseases formerly conceived as focal, such as myocardial infarction, have distributed effects throughout the body that are mediated through disease-specific networks (*15*). And finally, mental and societal stress triggers have been linked to various diseases associated with chronic inflammation that can be assessed already by WB-PET (*16*).

Inter-organ networks through PET

Current multi-organ network investigations using WB- or TB-PET are mostly fishing expeditions, aiming to pinpoint stable correlations between organs (*10,11*). In general, correlation analyses explore gross systemic effects between two groups without causal explanation. When performing correlation analyses, the chosen sample should represent the investigated population (e.g., healthy or pathological)

(*17*). Other factors, such as variability, linearity, and variance of the samples must also be considered. Since most multi-organ correlation network studies seek to pinpoint monotonic relationships between investigated organs, Spearman correlation should be chosen over Pearson correlation, as it is non-parametric and insensitive to the linearity and homogeneity of the variance of observed data.

The ultimate goal of inter-organ analysis is to identify causal relationships between organs that can facilitate the development of impactful interventions in medicine. Here, structure learning of Bayesian networks (*18*) in combination with graph models as visual representations of causal links in complex processes can be an attractive approach (*19*), which, however, still mandates the integration of a clinical expert to denounce spurious causal links.

Both causal and correlation networks should be considered hypothesis-generating tools rather than tools that provide solid endpoints. Such hypotheses must be proven or disproven in rigorous validation studies (Fig. 2), whereby investigators should be conscious of the confounders affecting the accuracy of standardised uptake values (SUV) or kinetic parameters as part of a multi-organ analysis (*20*).

The promise of TB-PET

Despite the increasing installed base of TB-PET systems, the number of studies that explore TB-PET beyond dose reduction and higher throughput for the sake of assessing the human connectome studies is limited. Preliminary studies have demonstrated the potential of using the temporal domain, namely raw time-activity curves, to derive metabolic associations between different bone compartments (*21*), or to construct normative networks for healthy male and female controls (*22*). Although neither study explained causality, dynamic TB-PET has the potential to create personalised causal networks from a single subject. Such a paradigm requires, however, the subject to be challenged by a task, pharmacological intervention, or external stressor (e.g., pain, cold). By challenging (perturbing) the

system, simultaneous or delayed changes in signals from different organs can be measured and used to establish causality.

For decades, such studies have been performed with functional MRI to derive effectivity connectivity by conducting baseline and task paradigms in a single imaging session (*23*). Recent innovative brain studies in functional PET have shown the possibility of using [18F]FDG PET to study dynamic changes in glucose metabolism within a single session with the aid of constant infusion protocols (*24*). However, conducting such challenge-based studies is non-trivial in a TB-PET setting, particularly in view of unknown response times and downstream interactions. Therefore, *test studies* on well-understood paradigms (*25*) should be performed before conducting exploratory connectome investigations using TB-PET.

Roadmap to the future: Connect to the connectome

To date, the PET imaging community is fragmented by vendor, geography and skillset. There needs to be more meaningful sharing of code, data and expertise to address the novel challenges and opportunities that arise with this technology. To fully leverage the potential of WB- and TB-PET alike for healthcare, new analysis methods are required, and new skills in the workforce are needed (*Fig. 2*). Automated data analytics pipelines, including automatic whole-body semantic segmentation (*26*) as well as WB- and TB-PET motion correction and spatial normalisation are prerequisites to robust TB-PET connectome studies.

The community needs to open up to repurpose existing solutions (e.g., SPM12 (*27*)) and to be prepared to fail in this high-risk-high-gain approach to using PET far away from the comfortable notion of a high-sensitivity lesion tracker. Fostering rigorous experiments to prove the validity of correlations and causalities while sharing also negative results must be encouraged. Also, rich data from healthy and pathological cohorts should be pooled to amass large sample sizes that help better understand the actual distribution of the data and, therefore, aid in arriving at logical conclusions.

Summary

The introduction of TB-PET offers unique opportunities to investigate multi-organ interactions - the organ connectome for understanding human physiology and pathology. Novel study protocols and paradigms, and translational research pipelines, will be required to support causal interpretations of inter-organ relationships. As a community, we should unite to prioritise progress over our vanities. The same was said in the early days of PET/CT and PET/MR, and it still holds true. Novel and open-minded collaborative efforts beyond the nuclear medicine comfort zone are required to unlock the power of WB- and TB-PET imaging. Adopting this concept requires significant personal and infrastructural investments; the concept may fail, but if it does not, it will benefit our patients and medicine at large.

DISCLOSURE

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FIGURES

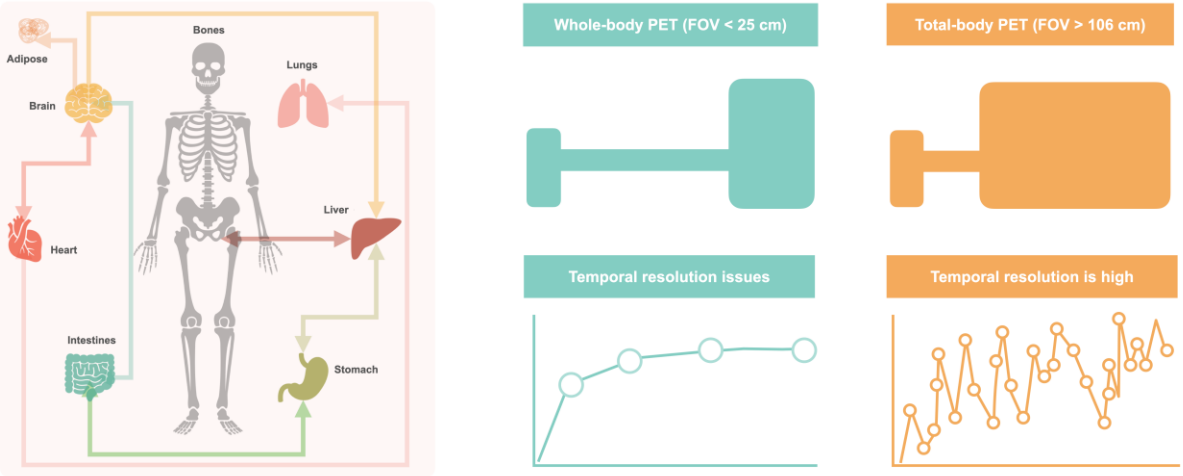

FIGURE 1. Thanks to the markedly increased performance, TB-PET allows the assessment of multiple organs synchronously, giving way to the non-invasive exploration of systemic, inter-organ interactions.

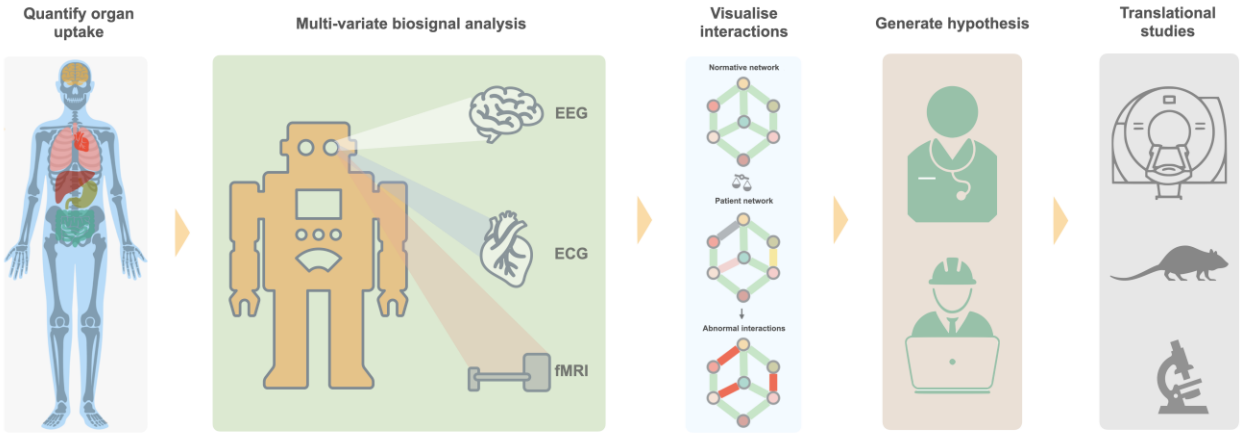

FIGURE 2. Categorical pathway to adopting whole-body/total-body PET for exploring the human connectome: several advanced and automated tools are required to extract robust data for hypothesis building and validation in a translational setting.

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