Carlos Morra: Biomarkers to replace clinical endpoints for the generation of diagnostic hypotheses with the potential to guide the development of novel psychotherapeutic drugs

MRI, PET and combined PET/MRI use in mental health research and diagnosis

Neuropsychiatric disorders have been studied for many years using neuroimaging biomarkers (Etkin 2019). They constitute a vital source of in-vivo evidence of pathological phenomena, with many heuristic applications for clinicians and researchers in mental health (Etkin 2019). However, only a few diagnostic classifications include them as criteria for diagnosis and, many psychiatrists have been reluctant to incorporate them in their practice because they feel unable to directly correlate abnormal results with diagnosis or treatments (McRobbie, Moore and Graves 2017; Etkin 2019).

This essay will briefly describe some of the current structural magnetic resonance imaging (sMRI) and positron emission tomography (PET) applications in mental health and research, analyse their advantages and disadvantages and introduce the benefits of combining both techniques. Finally, we will review their application for studying Alzheimer's disease (AD).

One of the most frequently used imaging techniques worldwide is sMRI (McRobbie, Moore and Graves 2017). It is an in-vivo morphological non-invasive diagnostic technique with several advantages, like a marked soft-tissue discrimination

capability with high spatial resolution, unlimited tissue penetration, which does not use ionizing radioactivity (Smith-Bindman, Miglioretti, Johnson et al. 2012; Lu and Yuan 2015; Wibawa, Rego, Velakoulis et al. 2019). Nevertheless, it has several limitations, especially in psychiatry such as, the duration of the study that might be a barrier for agitated, dyskinetic, or psychotic patients; the noise or the confined space limits the accessibility of overweighted, claustrophobic, or psychotic patients; finally, metallic prosthetics or implants, including vagus nerve stimulators contraindicates its use (Lu and Yuan 2015; Wibawa, Rego, Velakoulis et al. 2019).

International diagnostic classifications of mental disorders, such as DSM-5 or ICD-11, require for most disorder categories' diagnosis overruling organic brain disorders, making sMRI a valid instrument for this purpose (American Psychiatric Association 2013). Moreover, many researchers have suggested their usefulness in diagnosis, reporting specific structural abnormalities in MRIs in neuropsychiatric disorders such as mood disorders, panic, PTSD, obsessive-compulsive disorders, ADHD and schizophrenia (see Table 1) (Eliez and Reiss 2000; Nagai, Kishi and Kato 2007; Cherkasova and Hechtman 2009; Kang, Lee and Lee 2017). The contradictory results reported were not surprising, as many disorders are heterogenic with multiple subtypes with different onsets, symptomatology and outcomes (Shenton, Dickey, Frumin et al. 2001).

TABLE 1.	*reported sMRI findings in psychiatric diagnoses*	
Diagnosis	*Findings*	*Author*
MDD	Decreased volume in VMPFC, ACC, and hippocampus	Han et al., 2019
Bipolar D.	Decreased volume in VLPFC, OFC, insula, temporal regions, amygdala and hippocampus.	Horosawa et al., 2009
Panic D.	Decreased thickness in temporal lobe, insula and pars triangularis	Kang et al., 2017
PTSD	Decreased volume of the amygdala and hippocampus; ACC, and decreased gray matter densities	Nisar et al., 2020
OCD	Abnormalities in basal ganglia, thalamus, OFC, ACC, and insula	Yildiz et al., 2019
Somatoform disorders	Reduced volumes: cerebellum, amygdala and pituitary Increased volumes: cingulate cortex, middle frontal and angular gyrus	Rosetti et al., 2021
ADHD	Decreased volume in PFC, caudate, pallidum, accumbens, amygdala, hippocampus, and putamen	Chersova et al., 2009; Albajara Sáenz et al., 2019
Schizophrenia	Decreased brain volume, lateral, third ventricles enlargement, abnormalities in medial temporal lobe (amygdala and hippocampus) PFC, OFC, supramarginal,, angular gyri, basal ganglia, corpus callosum, thalamus, and cerebellar	Shenton et al., 2001; Kasai et al., 2002; Winton-Brown and Kapur, 2009
Alzheimer´s	Hippocampal, entorhinal cortex atrophies, reduced brain volume	Matsuda, 2016

PET imaging constituted a significant advance for psychiatric research that opened the possibility to study in-vivo functions and metabolism of structures like receptors or specific areas of the brain, making complex etiopathogenic mechanisms of CNS disorders accessible for understanding (Beaurain, Salabert, Ribeiro et al. 2019; Hellwig and Domschke 2019). Besides, it helped to study many pharmacological compounds' mechanisms of action and their role in either pathophysiology or therapeutics (Beaurain, Salabert, Ribeiro et al. 2019). It is considered a high sensitivity and penetration depth research instrument, with full-body imaging capabilities valuable for assessing functional changes that usually precede the organic ones (Lu and Yuan 2015; Wibawa, Rego, Velakoulis et al. 2019). However, several challenges for its implementation exist; many are related to PET being an invasive procedure with limited spatial resolution, whose imaging centers need to be close to a cyclotron; that requires the use of multiple short half-life radioactive tracers with different sensitivity and biological hazards and, of

course, the cost of the equipment and each study (Okamura, Harada, Furumoto et al. 2014; Lu and Yuan 2015; Knopman et al., 2018; Wibawa, Rego, Velakoulis et al. 2019; Sato, Mano, Suzuki et al. 2019). In addition to its invasive nature, data acquisition is a prolonged duration motion-sensitive process in a confined environment limiting the feasibility for many claustrophobic, psychotic, or agitated patients (Vadakkan and Siddiqui 2021; Steib, Schwartz, Stojeba et al. 1994).

PET is considered helpful for investigating psychiatric disorders such as schizophrenia, depression, bipolar disorder, anxiety disorders, somatoform disorders, ADHD and substance abuse disorders (See Table 2) (Ketter and Wang 2002; Sundaram, Chugani and Chugani 2005; Hosokawa, Momose and Kasai 2009; Huang, Ren, Jiang et al., 2020). Identifying receptors, areas and immune responses involved in these diseases' pathogenesis is crucial for understanding their role in the disease's pathophysiology and identifying treatment targets and treatment-resistant phenotypes (Demjaha, Murray, McGuire et al. 2012; Howes and Kapur 2014; Coughlin, Horti and Pomper 2019). Pharmaceutical and clinical researchers have adopted PET imaging to estimate psychotropic medications' receptor binding profiles (Arakawa, Takano and Halldin 2020). Using PET ligands that bind to enzymes, receptors or, transporters assist in identifying the mechanisms of action, the potency, the side effect profile of medications and substances of abuse (Weinstein, Livny and Weizman 2016; Beaurain, Salabert, Ribeiro 2019; Narayanaswami, Drake, Brooks et al. 2019; Arakawa, Takano and Halldin 2020; Navarrete, García-Gutiérrez, Jurado-Barba et al. 2020). Besides, targeting the translocator protein (TSPO) helps assess phenomena associated with neuroinflammation, associated with many psychiatric diseases like depression or

schizophrenia (Pariante 2019; Fourrier, Singhal and Baune 2019; De Picker and Haarman 2021).

Table 2.	*PET abnormalities in psychiatric disorders*	
Diagnosis	***Findings***	***Authors***
MDD	Hypometabolism: frontal, left cingulate, temporal gyri, right insula, parietal lobules, and right occipital gyrus	Hosokawa et al., 2009; Wei et al., 2016
Bipolar Depression	Hypometabolism: frontal gyri, right cingulate, and parietal lobules	Hosokawa et al., 2009
GAD	Hypermetabolism: amygdala, occipital, right temporal lobe, and right precentral frontal gyrus	Wu et al, 1991; Shiori, 2010
Somatoform disorders	Hypometabolism in PFC, insula, temporal, and occipital lobe	Huang et al., 2020
ADHD	Abnormal dopamine transporter and receptor binding, and metabolism	Weyandt et al., 2013
Schizophrenia	Hypometabolism: frontal, temporal and cerebellum . Hypermetabolism: medial temporal, basal ganglia and left thalamic . Dopaminergic, glutamatergic, GABA abnormalities. Neuroinflamation	Seethalakshmi et al., 2006; Egerton et al., 2017; Hellwig and Domschke, 2019; Cheng et al., 2020; Kim et al., 2020
Alzheimer´s	Hippocampal hypometabolism, presence of Aß-Amyloid, presence of hyperphosphorylated tau, neuroinflammation	Chandra et al., 2019

Since 1990, combined PET/MRI have successfully integrated simultaneously and synchronously functional, biochemical or metabolic aspects of the brain with high-resolution morphologic images (Wehrl, Judenhofer, Wiehr et al. 2009; Aiello, Cavaliere, Marchitelli et al. 2018). The benefits of combining these techniques are that they can be performed in a single session, some technical aspects of sMRI or fMRI may improve the quality and activity localization capabilities of PET, reduce the radiation dose and the motion artefact and accurately estimate the delivery of the tracer for quantitative brain PET by measuring input of the internal carotid artery (Miller-Thomas and Benzinger 2017; Zhu and Zhu 2019). However, these scanners use is limited to medical centers with highly trained radiologists and

several of the correction techniques and algorithms still require validation (Miller-Thomas and Benzinger 2017).

The single and the combined use of PET and MRI constituted a leap forward for the study of Alzheimer's disease (AD), a disorder with identified pathological findings; In 2018, in-vivo imaging biomarkers were incorporated for its diagnosis by the National Institute on Aging and the Alzheimer's Association Research Framework by adopting A/T/N diagnostic criteria (Jack, Bennett, Blennow et al. 2018). Each of the letters stands for one of the primary disease phenomena, A for Amyloid, T for Phosphorylated-Tau and N for neurodegeneration, confirming their presence by biomarkers changes (Jack, Bennett, Blennow et al. 2016). For example, the evidence of amyloid deposits of the brain (A) can be established using amyloid PET or CSF Aß42 (Jack, Bennett, Blennow 2016), Tau (T) abnormalities by assessing CSF phospho-tau or by Tau PET and neurodegeneration (N) by measuring CSF total-tau, by MRI, or fluorodeoxyglucose (FDG) PET (Lu and Yuan 2015; Cummings 2019). The results obtained following these guidelines provided helpful evidence for AD staging; thus, patients in the preclinical or prodromal phase could receive early diagnosis and treatment (Knopman, Haeberlein, Carrillo et al. 2018; Allegri, Pertierra, Cohen et al. 2019). Furthermore, combined PET/MRI opened new possibilities for diagnosis and severity assessment; for dementia research, it facilitated analyzing the relationship between several pathological findings, such as changes in glucose metabolism and cerebral blood flow (Tiepolt, Rullmann, Jochimsen et al. 2020; Yang and Zhang 2016).

In conclusion, structural sMRI, PET and combined PET/MRI provided helpful in-vivo structural and functional evidence for clinical psychiatry and research for studying multiple disorders. They share several advantages, but some limitations make it almost impossible to use them in certain mental conditions. However, a more significant limitation is that most clinical psychiatrists are still hesitant to incorporate them into their practices for not having a clear idea about the clinical implications or the necessary corrective actions when confronting an abnormal result. However, their utilization in psychopharmacological and neurophysiological research provided vital information for developing newer therapeutic interventions.

International diagnostic criteria of disorders seem to be adopting these neuroimaging biomarkers in their classifications, such as the A/T/N for AD diagnosis, gradually helping mental health professionals to accept the inevitable change.

In the future, with the improvement of existing technology, the incorporation of newer statistical methods and worldwide databases, we can foresee a substantial increase in acceptability and application (Lozupone, Seripa, Stella et al. 2017).

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