Applicability, potential and limitations of TSPO PET imaging as a clinical immunopsychiatry biomarker

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Abstract (249 words):

Purpose: TSPO PET imaging may hold promise as a single-step diagnostic work-up for clinical immunopsychiatry. This review paper on the clinical applicability of TSPO PET for primary psychiatric disorders discusses if and why TSPO PET imaging might become the first clinical immunopsychiatry biomarker and the investment prerequisites and scientific advancements needed to accomodate this transition from bench to bedside.

Methods: We conducted a systematic search of the literature to identify clinical studies of TSPO PET imaging in patients with primary psychiatric disorders. We included both original case-control studies as well as longitudinal cohort studies of patients with a primary psychiatric diagnosis.

Results: 31 original studies met our inclusion criteria. In the field of immunopsychiatry, TSPO PET has until now mostly been studied in schizophrenia and related psychotic disorders, and to a lesser extent in mood disorders and neurodevelopmental disorders. Quantitative TSPO PET appears most promising as a predictive biomarker for the transdiagnostic identification of subgroups or disease stages that could benefit from immunological treatments, or as a prognostic biomarker forecasting patients' illness course. Current scanning protocols are still too unreliable, impractical and invasive for clinical use in symptomatic psychiatric patients.

Conclusion: TSPO PET imaging in its present form does not yet offer a sufficiently attractive cost-benefit ratio to become a clinical immunopsychiatry biomarker. Its translation to psychiatric clinical practice will depend on the prioritising of longitudinal research and the establishment of a uniform protocol rendering clinically meaningful TSPO uptake quantification at the shortest possible scan duration without arterial cannulation.

Keywords: biomarker, translocator protein, positron emission tomography, psychiatry, nuclear imaging

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1. Introduction

More than two decades of neuroimaging research have provided valuable leads into the neurobiological underpinnings of major psychiatric disorders. Regrettably, these scientific advances have thus far not resulted in significant improvements of diagnostic accuracy or treatment response for the individual patient. Unlike clinical practice in neurology, neuroimaging is currently not recommended in US or EU practice guidelines for any primary psychiatric disorder, except for the exclusion of potentially underlying medical conditions on a case-by-case basis.[1]

Positron emission tomography (PET) imaging with ligands targeting the translocator protein (TSPO) has been developed as a method to evaluate *in vivo* glial responses related to neuroinflammation. Serendipity caused the advent of this new nuclear imaging application to coincide with the rise of immunopsychiatry, an emergent discipline concerned with the study of immunological pathways in major psychiatric illness.[2] Convincing evidence from genome-wide assays, epidemiological studies and randomized controlled trials all point towards immune system involvement in a wide range of psychiatric conditions including psychotic disorders, mood disorders and autism spectrum disorders.[3]. Previously, the study of central nervous system (CNS) immune activity in psychiatric patients was limited to scarcely available CFS samples or *post-mortem* brain tissue. The development of TSPO PET has allowed for the first time to not only visualize, but also quantify neuroinflammation *in vivo* and has therefore justifiably attracted great interest from immunopsychiatry researchers worldwide. Notably, schizophrenia was among the first disorders to be investigated in a clinical study with TSPO PET.[4] In the early stages of TSPO PET research, some authors as well as nuclear ligand patent holders optimistically anticipated this breakthrough molecular imaging technique would soon develop into successful clinical applications for the diagnosis and treatment of patients with diverse brain disorders.[5, 6] Quantitative TSPO PET results were projected as biomarkers (i.e. biological markers) for the extent of cerebral inflammation and even as a surrogate to monitor disease progression in neurodegenerative disorders across the field of neurology, neuro-oncology and psychiatry.[7, 8]

Undoubtedly the need for good clinical biomarkers in psychiatric illness is both valid and urgent. The lack of good surrogate endpoints or stratification markers for clinical trials has withered down drug development investments after too many late-stage failed drug trials. Even more critical, psychiatric nosology and diagnosis has come to a standstill with clinical decision making in psychiatry still mostly relying on empirical trial and error processes, consuming patients' valuable time and quality of life.[1] Impediments against biomarker development for psychiatric disorders include our limited understanding of psychiatric pathophysiology, obscuring the link between abnormal biological test results and the pathogenesis of psychiatric symptoms, as well as the relative inaccessibility of brain tissue and insufficient knowledge about the bidirectional relationships between peripheral and central biological changes. Furthermore, research targeting diagnostic biomarker development has been frustrated by the lack of a gold standard diagnostic test to confirm psychiatric diagnoses, while current criteria-based classifications are inadequate to distinguish overlapping or comorbid conditions.[9] Finally, the long-term use of psychopharmaceutic compounds by a large number of patients can also confound study results.

Given all of the above, there are good reasons why TSPO PET imaging may hold promise as biomarker for immunopsychiatry, and good reasons to carefully consider the investment prerequisites and scientific advancements needed to accommodate this transition from bench to bedside. Most previous reviews on this subject have focused on the theoretical foundations and scientific validity of TSPO protein as biomarker of neuroinflammation[10], while little to no attention has been given to weighing the pros and cons of performing TSPO PET imaging in the real-life clinical context of psychiatric patients. In this review paper on the clinical applicability of TSPO PET for primary psychiatric disorders, we will argue if and why TSPO PET imaging might become the first clinical immunopsychiatry biomarker, and potential barriers it will need to overcome to do so.

2. Method

We conducted a systematic search of the literature to identify clinical studies of TSPO PET imaging in patients with major psychiatric disorders. We performed a wide Pubmed search on September 30th 2020 using search string (((TSPO[Title/Abstract] OR translocator protein[Title/Abstract] OR pbr[Title/Abstract] OR peripheral benzodiazepine receptor[Title/Abstract] OR microglia*[Title/Abstract])) AND (PET[Title/Abstract] OR MR-PET[Title/Abstract] positron emission tomography[Title/Abstract])) AND (brain[Title/Abstract] OR CNS[Title/Abstract] OR central nervous system[Title/Abstract] OR psychiatric[Title/Abstract] OR neuropsychiatric[Title/Abstract] OR schizo*[Title/Abstract] OR psycho*[Title/Abstract] OR

depress*[Title/Abstract] OR bipolar[Title/Abstract] OR autism[Title/Abstract] OR ADHD[Title/Abstract] OR posttraumatic stress[Title/Abstract] OR anxiety[Title/Abstract]), with application of filter Language (English), without limitation of Publication Date. We included both original case-control studies as well as longitudinal cohort studies of patients with a primary psychiatric diagnosis. On account of the explicit clinical angle of this review, we excluded studies without human participants or which only reported on PET methodology or the correlation between TSPO PET and other, non-clinical, biological measures (e.g. findings from structural or functional MRI, magnetic resonance spectroscopy or blood-based measures). Primary psychiatric disorders were defined as schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder and other psychotic disorders, as well as ultra-high risk states), mood disorders (major depressive disorder, bipolar disorder), anxiety and stress-related disorders (including obsessive-compulsive disorder and posttraumatic stress disorder) and neurodevelopmental disorders such as autism spectrum disorder and Tourette's disorder. Of note, a number of studies have investigated TSPO PET binding in current and recently abstinent substance use disorder patients as well as patients with (an increased risk of) psychiatric symptomatology (such as chronic pain or a history of childhood maltreatment or other psychosocial risk factors) but we considered these to lie beyond our current scope.

3. Results

Out of 775 original hits, 32 research papers reporting on 31 original studies met our inclusion criteria, five of which were published within the last year (2020). In the field of immunopsychiatry, case-control TSPO PET studies have until now mostly been used in schizophrenia or related psychotic disorders (16 case-control studies [4, 8, 11-25]; previously reviewed elsewhere[26-28]), and to a lesser extent in mood disorders with seven case-control studies in major depressive disorder [29-35], two longitudinal studies of depressed patients [36, 37] (MDD; previously reviewed elsewhere[10, 38]), and one case-control study in euthymic bipolar disorder patients [39]. A further two studies have been performed in autism spectrum disorders [40, 41], one study in Tourette's disorder [42], one study in obsessive-compulsive disorder (OCD)[43] and one study in posttraumatic stress disorder (PTSD)[44]. (cfr Table 1). The mean patient sample size was 20.7±11.9 and has increased significantly over time ($F=5.95$, $p=0.022$). 65.5% of studies used an arterial plasma input function for PET kinetic modelling. Mean scan duration was 90.1±27.0 minutes. There were no significant differences between studies in mood disorders versus psychotic disorders in terms of patient sample size (23.8±17.5 vs. 19.8±10.5, $t=0.726$, $p=0.476$), arterial line use (75.0% vs. 68.8%, $\chi^2=0.101$, $p=0.751$) or scan duration (97.5±29.6 vs. 85.4±7.2, $t=1.014$, $p=0.323$). The most popular tracers were [^{11}C]PK11195 (12 studies), [^{18}F]FEPPA (9 studies) and [^{11}C]PBR28 (7 studies), while [^{18}F]PBR111, [^{11}C]DPA713 and [^{11}C]DAA1106 were each used in only one study.

4. Discussion

4.1. The promise of TSPO PET biomarkers in clinical immunopsychiatry

The National Institutes of Health define a biomarker as 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention.'[45, 46] Biomarkers can be of a diagnostic, prognostic, predictive or pharmacodynamic nature or serve as surrogates (i.e. replacing the clinical endpoint in a trial).

A valid *diagnostic biomarker* needs to demonstrate at least 80% sensitivity and 80% specificity for detecting a certain disease from controls, and in distinguishing the illness from other relevant differential diagnoses.[1] Given the large range of psychiatric conditions in which some degree of neuroinflammation and increased TSPO binding is expected and observed, it is unlikely TSPO PET could ever be developed as a biomarker to support psychiatric diagnostic processes in the categorical sense. However, building on a dimensional diagnostic approach, as previously proposed by the RDoC framework, it could be used to identify a relevant subgroup of patients: those with increased neuroinflammation. In turn this could inform clinicians about a patient's chance of responding to anti-inflammatory treatment (*predictive biomarker*) or their expected illness course (*prognostic biomarker*). One such example has been a recent study in which MDD patients with increased TSPO binding at baseline demonstrated larger clinical effects after 8 weeks treatment with the non-steroidal anti-inflammatory drug celecoxib[36] It is important to note that this study was lacking a placebo arm and subjects were not prospectively stratified based on TSPO uptake, limiting its clinical usefulness at this time. Further stratified randomized controlled trials will be needed to determine if quantitative TSPO PET results can reliably predict treatment response with anti-inflammatory or psychiatric interventions. In neuropsychiatric disorders, the predictive and prognostic value of TSPO PET in diseases characterized by abnormal glial functioning has been demonstrated in longitudinal studies of Alzheimer's disease [47, 48] and multiple sclerosis [49-51] patients. This type of follow-up studies is currently lacking for psychiatric disorders in the strict sense, but could hold promise for early detection

and preventive treatment of those at risk of a more ulterior illness progression. In a case reported by Bloomfield et al., the patient with the highest TSPO binding among a cohort of ultra-high risk individuals was the first to convert to full-blown schizophrenia[11] If molecular imaging with could detect functional change preceding overt psychopathology, early diagnosis and treatment could prevent further neurotoxicity and clinical deterioration. However, other TSPO PET studies in individuals with ultra-high risk for psychosis have not been able to demonstrate significant group differences from age-matched healthy controls.[15, 18]

The development of TSPO PET as either a predictive or prognostic biomarker requires longitudinal studies (*predictive*: minimum 8-12 weeks pre-post interval for most interventions; *prognostic*: follow-up period months-years). To our knowledge only four longitudinal TSPO PET studies have been conducted in psychiatric illness, of which two were published in the last year.[22, 36, 37, 41].Interestingly, in these longitudinal studies TSPO PET was able to show greater efficacy of celecoxib for the treatment of depression in individuals with more neuroinflammation and demonstrate a decrease of neuroinflammation during psychotherapy.[36, 37] Given adequate funding, this methodological design is feasible and should be prioritised for further research in psychiatric illnesses.

The relationship between peripheral immunological aberrations and neuroinflammation is a complex one.[52] Immune competent glial cells have more complex functions than other tissue macrophages.[53] Furthermore, neuroinflammation has a bidirectional relationship with the blood brain barrier,[54] and this interaction is modulated by the microbiome and the vagus nerve, as well as peripheral circulating cytokines.[55] Compared to potential peripheral immunological biomarkers, CNS biomarkers such as TSPO PET imaging have a closer proximity to neuropsychiatric pathophysiological processes. In view of the current absence of reliable biomarkers, undoubtedly any development that leads to better staging and improved patient management is worth pursuing. Detection of neuroinflammation through TSPO PET relates to an underlying process, which is not confined by the traditional categorical classification system and therefore not hindered by the typical clinical fluidity and diagnostic uncertainty, while also facilitating the repurposing of an array of anti-inflammatory treatments. Quantitative TSPO PET could therefore bring a single-step diagnostic work-up for the transdiagnostic identification of subgroups or disease stages that would benefit from treatment targeting the immune system, regardless of clinical psychiatric diagnosis[56]

4.2. Three translational gaps between scientific aspirations and clinical reality

4.2.1. The reliability gap: heterogeneity and test-retest reproducibility

While TSPO PET imaging may be less hindered by clinical heterogeneity, methodological and biological variability has complicated the study of psychiatric patients with TSPO PET, in particular those with psychotic disorders such as schizophrenia. Remarkably, first-generation TSPO tracers, e.g. [^{11}C]PK11195, tend to yield an increased signal [28], whereas second-generation tracers, e.g. [^{11}C]PBR28 or [^{18}F]FEPPA, have overall found a decreased TSPO PET signal [26, 57] in schizophrenia patients compared to healthy age-matched controls. Similarly, mixed results have come from the study of ASD patients.[40, 41]. The controversy surrounding the causes of these mixed results in schizophrenia and psychotic disorders has subsequently instigated questions about fundamental gaps in our knowledge of neuroinflammatory pathophysiology and criticism about the validity of the TSPO protein as a target.[27, 58-60] Rather than representing microglial activation per se, TSPO PET uptake probably reflects a broader spectrum of glial responses from multiple cell types, including microglia, macrophages, and astrocytes, as well as a low-level physiological expression in vascular endothelial cells.[61, 62] Although these and other more technical aspects of TSPO PET imaging are beyond the scope of this article, recent evidence does confirm that, although TSPO expression is not microglia-specific, TSPO imaging specifically reveals the pro-inflammatory phenotype of activated glial cells in response to certain inflammatory stimuli, and can therefore indeed be considered to reflect neuroinflammation in some – but not all - conditions.[62, 63] Further research is needed to fully grasp the factors affecting TSPO expression patterns and their functional significance.[62] To complicate matters further, high levels of peripheral CRP have recently been demonstrated to limit TSPO radioligand perfusion into and from the brain parenchyma in depressed patients and in healthy controls, which could cause influence TSPO kinetic modelling.[64] Before any steps can be taken to develop TSPO PET as a valid clinical biomarker, all methodological sources of variability need to be cancelled out through robust standardisation of the methodology resulting in a uniform protocol. Admittedly, a more reliably signal has come from the study of mood disorders, with patients during a current depressive episode demonstrating increased TSPO binding, which is highest in patients who were unmedicated at the time of the scan and in patients who had untreated MDD for 10 years or longer.[10] Preliminary results from other conditions have also pointed towards

increased TSPO binding in OCD and in bipolar disorder patients during the euthymic state but decreased binding in PTSD. Surprisingly, while psychotic and neurodevelopmental disorders have been more strongly linked to immunogenetic vulnerability, stress-related internalizing or "neurotic" disorders (MDD, OCD, chronic pain disorders) are generating the stronger TSPO neuroinflammatory signal and it may thus be wise to prioritise these disorders for TSPO biomarker development. However, this conclusion may be confounded by the nature of the patients with psychotic disorders who have been studied with TSPO PET (less acutely symptomatic) and is likely premature given the small sum of patients with non-psychotic disorders studied.

Given that the most promising avenue for the clinical development of TSPO PET lies in its use as a predictive or prognostic biomarker, its test-retest reproducibility in longitudinal studies is of the utmost importance. Unfortunately, several authors have demonstrated TSPO PET test-retest properties to be suboptimal, even in healthy controls (ICCs ranging from 0.47-0.92 for cortical gray matter regions and 0.06-0.90 for smaller regions) and influenced by circadian rhythm effects.[23, 65] For clinical studies, this means statistical power is reduced and larger sample sizes will be required. In the clinical setting, alterations observed over time in an individual patient may be misinterpreted or not detected at all.

4.2.2. The generalisability gap: influence of clinical confounders and psychotropics

A second major problem for the clinical translation of TSPO PET is the limited generalisability of findings from highly selected research cohorts to real-life clinical populations. Firstly, we will need a much better understanding of the impact of certain confounders which are of particular importance to psychiatric patients, most notably toxic influences, e.g. smoking, cannabis and substance use, and metabolic effects, measured as body mass index and blood-derived metabolic biomarkers.[27, 66] Secondly, a huge unresolved problem is the influence of current or previous exposure to psychotropic drugs and other psychoactive substances which can either directly affect translocator protein binding (benzodiazepines or Z-drugs) or indirectly alter peripheral and CNS inflammatory processes (atypical antipsychotics [67, 68], lithium [69] and antidepressants). From the limited number of clinical studies investigating both unmedicated and medicated patients, opposite effects are observed for the use of antidepressants in MDD versus antipsychotics in schizophrenia patients. [19, 32] These barriers can only be overcome by studying larger groups of patients, which will be a challenging endeavour, given the cost and time-intensive nature of this type of research.

4.2.3. The feasibility gap: burden to patients and psychiatric healthcare providers

TSPO PET scanning protocols do not only need to become more uniform and reliable, but also much more patient-friendly than they have been so far. In particular for patients in acutely distressed mental states, scanning protocols need to be minimally invasive, without arterial cannulation and with the shortest possible scanning duration. In our own work, we have seen a significant proportion of subjects who were ineligible or excluded due to movement artefacts or difficulty with arterial cannulation. Furthermore, some authors have stated ethical concerns about arterial cannulation in low-functioning participants who may require surrogate consent.[41] In particular in such acutely or severely ill psychiatric patients, prolonged scanning protocols (typically 60-125 minutes) are equally unworkable without the use of sedatives. However, both benzodiazepines and propofol have been demonstrated to influence TSPO binding in the human brain.[70] Short-acting barbiturates (IV Nembutal) have been used in one study – reporting 14 out of 28 children aged 11+/-3 years old required sedation for the TSPO PET intervention.[42] Some studies have sought to overcome this problem by having a trained healthcare professional stay in the PET room with the patient throughout the duration of the procedure, or by providing participants a training protocol consisting of videos demonstrating the procedures and/or undergoing a training scan.[41, 71] Future clinical TSPO PET scanning protocols will therefore also need to include guidelines on recommended use of anxiety-reducing methods. Complicating matters even further, most second-generation tracers are affected by a polymorphism located in exon 4 of the *TSPO* gene, resulting in a nonconservative alanine to threonine substitution at position 147 (Ala147Thr; i.e. rs6971 polymorphism) in the fifth transmembrane domain of the TSPO protein.[72] Not only does this require prior genotyping of participants, in those homogeneous to the Thr/Thr haplotype (so-called 'low-affinity binders', estimated at around 10% of the Caucasian population) the biomarker would simply not work. Efforts should be made to avoid this additional barrier by prioritising tracers less affected by this polymorphism, or by the use of kinetic modelling outcomes which quantify relative (e.g. DVR) rather than absolute (e.g. V_T) tracer uptake. Equally problematic, any TSPO PET quantification method without arterial input function requires MRI co-registration to extract a pseudo-reference region. As integrated MR-PET scanner availability is still scarce, the diagnostic work-up thus inflates to a two-step process consisting of a separate PET and MRI scan, requiring planning, transportation and supervision efforts by the clinical psychiatric staff.

5. Conclusion

We conclude that TSPO PET imaging in its present form does not offer a sufficiently attractive balance for clinical application in psychiatric disorders. Current scanning protocols are still too unreliable, impractical and invasive for clinical day-to-day use in symptomatic psychiatric patients, and the potential therapeutic benefits of TSPO uptake quantification do not outweigh the additional burden imposed on an individual patient. The translation of this imaging application to clinical practice will depend on the prioritising of longitudinal clinical research and our ability to establish a uniform and solid TSPO PET protocol rendering clinically meaningful results at the shortest possible scan duration without arterial cannulation. Conceivably, more reliable and/or readily accessible markers will be identified in parallel and substitute TSPO PET imaging as the primary predictive and/or prognostic biomarker for immunopsychiatry. Already, predictive serum correlates of TSPO PET uptake and promising new targets are being investigated for this purpose.[10, 73] Results from a recently published randomized clinical trial indicate that even a readily accessible marker like serum C-reactive protein could be used as predictive biomarker to stratify patients with MDD who could benefit from antidepressant augmentation with minocycline.[74] We would therefore postulate that TSPO PET will remain but a valuable research application for the field of immunopsychiatry.

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Code availability: Not Applicable

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Table 1

Case-control studies						
Author year	*Diag-nosis*	*Sample size*	*PET tracer*	*Arterial cannu-lation*	*Scan duration*	*Outcome*
Mood disorders						
Haarman 2014[39]	BD euthymic	14 P 11 HC	[^{11}C]PK11195	Y	60	↑
Hannestad 2013[29]	MDD	10 P 10 HC	[^{11}C]PBR28	Y	120	=
Holmes 2018[30]	MDD	14 P 13 HC	[^{11}C]PK11195	N	60	↑
Li 2018[31]	MDD	50 P 30 HC	[^{18}F]FEPPA	Y	125	↑
Richards 2018[32]	MDD	28 P 20 HC	[^{11}C]PBR28	Y	90	↑ unmed = med
Setiawan 2015[33]	MDD	20 P 20 HC	[^{18}F]FEPPA	Y	125	↑
Setiawan 2018[34]	MDD	50 P 30 HC	[^{18}F]FEPPA	Y	125	↑
Su 2016[35]	MDD	5 P 13 HC	[^{11}C]PK11195	N	75	↑
Psychotic disorders						
Banati 2009[8]	Sz	16 P 8 HC	[^{11}C]PK11195	N	N/R	↑
Bloomfield 2016[11]	Sz chron	14 P 14 HC	[^{11}C]PBR28	Y	90	↑
	Sz UHR	14 P 14 HC				↑
Collste 2017[12]	Sz FEP	16 P 16 HC	[^{11}C]PBR28	Y	91	↓
Conen 2020[13]	Sz recent-onset + chron	41 P 21 HC	[^{11}C]PK11195	N	60	=
Coughlin 2016[14]	Sz recent-onset	12 P 14 HC	[^{11}C]DPA713	Y	90	=
Di Biase 2017[15]	Sz chronic	15 P 12 HC	[^{11}C]PK11195	N	60	=
	Sz UHR + recent-onset	28 P 15 HC				=
Doorduin 2009[16]	Sz recent-onset	7 P 8 HC	[^{11}C]PK11195	Y	60	↑

Hafizi 2017[17]	Sz FEP	19 P 20 HC	[^{18}F]FEPPA	Y	125	=
Hafizi 2017(b)[18]	Sz UHR	24 P 23 HC	[^{18}F]FEPPA	Y	125	=
Holmes 2016[19]	Sz	16 P 16 HC	[^{11}C]PK11195	N	60	↑ med = unmed
Kenk 2015[20]	Sz active psychosis	27 P 16 HC	[^{18}F]FEPPA	Y	125	=
Laurikainen 2020[21]	Sz FEP	13 P 15 HC	[^{11}C]PBR28	Y	70	↓
Ottoy/De Picker 2018[22, 23]	Sz active psychosis	11 P 17 HC	[^{18}F]PBR111	Y	90	= <35y ↑ >35y
Takano 2010[24]	Sz chronic	14 P 14 HC	[^{11}C]DAA1106	Y	90	=
Van Berckel 2008[4]	Sz	10 P 10 HC	[^{11}C]PK11195	Y	60	↑
Van der Doef 2016[25]	Sz recent-onset	19 P 17 HC	[^{11}C]PK11195	N	60.5	=
Other disorders						
Attwells 2017[43]	OCD	20 P 20 HC	[^{18}F]FEPPA	Y	125	↑
Bhatt 2020[44]	PTSD	23 P 26 HC	[^{11}C]PBR28	Y	120	↓
Kumar 2015[42]	Tourette's disorder	12 P 15 HC	[^{11}C]PK11195	N	60	↑
Suzuki 2013[40]	ASD	20 P 20 HC	[^{11}C]PK11195	N	62	↑
Zürcher 2020[41]	ASD	18 P 15 HC	[^{11}C]PBR28	N	90	↓

Longitudinal studies

Author year	*Diag-nosis*	*Sample size*	*Tracer*	*Time points [interval]*	*Outcome*
Attwells 2020[36]	Treatment-resistant MDD	41 P	[^{18}F]FEPPA	T1=baseline T2=after celecoxib treatment [8w]	TSPO uptake predicted response to celecoxib
De Picker 2019[22]	Acute psychosis in SZ	10 P 16 HC	[^{18}F]PBR111	T1= baseline T2= after antipsychotic treatment [8w]	Patients' change in TSPO uptake over time was age-dependent
Li 2018(b)[37]	Newly diagnosed MDD	20 P CBT 20 P SPT 20 HC	[^{18}F]FEPPA	T1= baseline T2= after CBT	Increased baseline TSPO uptake decreased after CBT
Zürcher 2020[41]	ASD	8 P 10 C	[^{11}C]PBR28	T1= baseline T2= after 3 months [15w]	Lower TSPO uptake in patients was stable and replicable

Legend: BD=bipolar disorder; P=patients; HC=healthy controls; MDD=major depressive disorder; unmed=unmedicated patients; med=medicated patients Sz=schizophrenia spectrum disorders; FEP=(untreated) first episode psychosis; UHR=ultra-high risk/clinical high risk for psychosis; OCD=obsessive-compulsive disorder; PTSS=posttraumatic stress disorder; ASD=autism spectrum disorders; CBT=cognitive-behavioural therapy; SPT=supportive psychotherapy. N/R=not reported.