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Review

# Opportunities in precision psychiatry using PET neuroimaging in psychosis☆

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ABSTRACT

With the movement toward precision medicine in healthcare, recent studies of individuals with psychosis have begun to explore positron emission tomography (PET) as a tool to test for biochemical signatures that may distinguish subtypes of psychosis that guide subtype-specific therapeutic interventions. This review presents selected PET findings that exemplify early promise in using molecular imaging to predict treatment response, provide rationale for new therapeutic targets, and monitor target engagement in biomarker-defined subtypes of psychosis. PET data, among other data types, may prove useful in the scientific pursuit of identifying precision strategies to improve clinical outcomes for individuals with psychosis.

## 1. Introduction

Modern medicine emphasizes high-value precision care. The movement toward precision medicine recognizes the varied response to treatment among individuals with a shared condition, and promises to optimize the benefit-risk ratio of clinical care through an approach that "takes into account individual variability in genes, environment, and lifestyle for each person (ghr.nlm.nih.gov/primer/precisionmedicine/definition)." Individual data are used to stratify patients with a shared condition into clinically relevant groups that best predict prognosis and therapeutic outcomes.

In the context of treating patients with active psychosis, current clinical guidelines starkly contrast this precision approach. Clinicians universally consider prescription of an antipsychotic medication that antagonizes the dopamine D2 receptor (Talbot and Laruelle, 2002) for symptomatic relief. Addition of a mood-stabilizing or antidepressant medication is often considered if the working diagnosis is an affective psychosis. Unfortunately clinical diagnoses that are based on descriptive criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) rather than biological assessment often fall short of predicting the response to these conventional interventions (Pearlson et al., 2016). In practice, overall symptoms may lessen moderately with pharmacological D2 receptor blockade (Leucht et al., 2009), but many patients suffer from persistent negative symptoms (Fusar-Poli et al., 2015) that are linked to functional disability (Ventura et al., 2015) and too often individuals with psychosis prove resistant to conventional antipsychotic medication (Chakos et al., 2001).

The pursuit of precision care in psychosis offers hope for improved outcomes. However, the movement of precision efforts into fields outside of oncology is in its infancy. Even the fundamental assumptions on which this approach is based are broached in scientific discussions with cautionary tone (Colijn et al., 2017; Psaty et al., 2018). First, we must be able to stratify individuals by factors that influence or predict treatment response using available methods of data acquisition and analysis. Second, we need the best-fitting interventions for each stratified group. In treatment-resistant depressive conditions, findings from a recent proof-of-concept study suggest that a subgroup of patients with high inflammatory profile (readily measured in blood) uniquely experience reduced depressive symptoms from infusion of the available medication, infliximab, which antagonizes an inflammatory cytokine (Raison et al., 2013). In psychotic conditions, the repurposing of old therapies or development of new therapies will be guided best by the knowledge gained through the neurobiological signatures that define subtypes of psychosis. A multi-site consortium of investigators known as the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) is collecting and probing almost 50 biological measures that include outcomes from structural, diffusion-tensor, and functional imaging in order to identify biotypes in psychosis (Pearlson et al., 2016).

The aim of this concise review is to summarize recent, select efforts using molecular imaging to define subgroups of individuals with psychosis that are based on neurobiological signatures with relevance to treatment. The selected findings exemplify early promise in the utility

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of molecular imaging to predict treatment response, provide rationale for new therapeutic targets, and monitor target engagement in biomarker-defined subtypes of psychosis. Future research in precision psychiatry will likely benefit further from combining molecular imaging data with other data types (clinical, genomics, psychosocial, radiomics). Nevertheless, this review aims to spotlight recent positron emission tomography (PET) neuroimaging research that demonstrates how PET data may help reduce to practice the precision care approach for those suffering from psychosis.

## 2. Predicting treatment response to conventional antipsychotic medications using [$^{18}$F] DOPA PET

The theory of aberrant dopaminergic neurotransmission underlying psychosis is decades-old, with link to the current clinical use of pharmacological dopamine D2 receptor blockade for treatment (Talbot and Laruelle, 2002). However, as mentioned above, approximately one-third of patients with schizophrenia do not benefit from available antipsychotic medication and this treatment-resistant subtype may be associated with diverse genetic, clinical, social, and biological factors (Lindenmayer, 2000).

While efforts are under way to guide clinicians about best-treatment practices for this group (Nucifora Jr et al., 2018), one approach to understanding the neurobiochemical differences in individuals who respond to D2 blocking drugs from the non-responders is through use of PET. PET is a molecular imaging technique that allows the "visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems (Mankoff, 2007)." A radioligand is injected in a "tracer" dose to allow estimation of the density of a protein or the activity of a physiological process without producing a measurable pharmacological effect. PET is particularly useful in clinical neuroimaging research since it allows noninvasive, although indirect, cross-sectional and longitudinal study of biochemical changes in the living brain. Furthermore, the same radiotracers used in human PET can be applied to animal models with dedicated small animal PET, facilitating forward- and back-translational, complementary study of a targeted physiological process or protein.

Work using PET has identified a hyperdopaminergic phenotype within individuals with psychosis (Howes and Kapur, 2014) that may distinguish those that subsequently respond to conventional antipsychotic medication from the non-responders (Demjaha et al., 2012; Kim et al., 2017). That research used bolus injection of [$^{18}$F]DOPA, which is a radiolabeled substrate for amino acid decarboxylase. The normalized steady state uptake rate constant (Ki$^{cer}$) in associative striatum was proposed to reflect presynaptic dopamine synthesis capacity and availability of dopamine for release (DSC). Elevated DSC has been reported at onset of both affective and non-affective forms of psychosis (Jauhar et al., 2017), as well as in the clinical high-risk state for psychosis (Egerton et al., 2013; Howes et al., 2011). Building on cross-sectional work in chronic patients with treatment-resistant schizophrenia (Demjaha et al., 2012; Kim et al., 2017), Jauher et al. designed a prospective study of 26 unmedicated patients with first-episode psychosis and 14 controls who underwent [$^{18}$F]DOPA PET prior to initiation of a course (minimum 4 weeks) of conventional antipsychotic treatment (Jauhar et al., 2018). Ki$^{cer}$ was higher in antipsychotic responders, defined as improvement in the PANSS total score of > 50%, compared to non-responders or controls. Within patients, that putative index of striatal DSC was also positively correlated with improvements in positive, negative, and total symptoms assessed on the PANSS and negatively correlated with change in the global assessment of functioning (Jauhar et al., 2018). In summary, the findings by Jauher et al. suggest a subtype of psychosis with striatal dopamine dysfunction, detected with [$^{18}$F]DOPA PET, which is linked to antipsychotic treatment response.

If validated further, the stratification of patients by [$^{18}$F]DOPA Ki$^{cer}$ may have utility in guiding clinical decisions toward or away from use of a traditional D2 blocking antipsychotic medication (Howes and Kapur, 2014). The improved value in clinical care would stem from prudent avoidance of using conventional antipsychotic medication in individuals with low [$^{18}$F]DOPA Ki$^{cer}$, sparing them unnecessary side effects and delayed benefit in treatment. Instead, this group may be best treated using alternative therapies (Howes and Kapur, 2014; Kim et al., 2017) such as clozapine, which has a unique neuroreceptor binding profile (Nucifora Jr et al., 2017), brain stimulation, or psychotherapy.

A subgroup with psychosis and high [$^{18}$F]DOPA Ki$^{cer}$ may benefit not only from D2 antagonistic medications, but from disease-modifying strategies aimed at normalizing dopaminergic tone through targets mechanistically upstream of the high DSC. For example, recent investigations have focused on normalizing hippocampal hyperactivity that may drive the hyperdopaminergic tone in the associative striatum (Grace and Gomes, 2018). Activation of the α7 nicotinic cholinergic receptor (α7-nAChR) that is highly expressed on GABAergic interneurons in the hippocampus is one such approach. Using the methylazoxymethanol acetate (MAM) developmental disruption rodent model of schizophrenia, the effect of α7-nAChR agonism in ventral hippocampus normalized the responsivity of midbrain dopaminergic neurons that project to the associative striatum in the rodent (Neves and Grace, 2018). Through modulating downstream dopaminergic signaling, the α7-nAChR, particularly in hippocampus, is a promising pharmacological target in psychosis (Neves and Grace, 2018), which may prove most relevant for individuals with psychosis and high [$^{18}$F]DOPA Ki$^{cer}$. Since there are several hypothesized mechanisms for pre-synaptic dopamine dysfunction in psychosis (Howes and Kaar, 2018), it is also provocative to think that this subgroup with high [$^{18}$F]DOPA Ki$^{cer}$ may be subdivided further using markers of the varied biological (GABAergic, glutamatergic, cholinergic) and environmental (psychological stress, trauma) mechanisms upstream of high striatal DSC. Through better mechanistic understanding, preventative strategies such as activation of the α7-nAChR in the perinatal period (Ross et al., 2016) or other developmental stage may be pursued.

## 3. Informing medication trials targeting the α7-nAChR in psychosis using [$^{18}$F] ASEM PET

The α7-nAChR has been pursued as an alternative therapeutic target in psychosis based on converging evidence of its link to psychosis (Tregellas and Wylie, 2018). Postmortem immunohistochemical study of tissue from those with schizophrenia has revealed low density of the α7-nAChR in the hippocampus, a region where the α7-nAChR is usually more highly expressed (Schaaf, 2014), as well as low density in cingulate cortex, frontal lobe, and the reticular thalamic nucleus in schizophrenia (Court et al., 1999; Freedman et al., 1995; Guan et al., 1999; Marutle et al., 2001). Furthermore, genetic abnormalities on chromosome 15 that affect *CHRNA7*, which encodes the α7-nAChR, have been linked to neuropsychiatric phenotypes relevant to schizophrenia (Dempster et al., 2006; Leonard et al., 2002). Risk variants at 15q13.3 have been associated with schizophrenia (Lowther et al., 2015; Stefansson et al., 2008), and recent study of iPSC-derived neuronal progenitor cells from individuals with 15q13.3 microdeletion or microduplication support a resulting downregulation of α7-nAChR-dependent calcium signaling underlying the manifested neuropsychiatric phenotypes (Gillentine et al., 2017). Work in a mouse model of human 15q13.3 microdeletion syndrome (Fejgin et al., 2014) underscores a key, combined effect of hemizygous 15q13.3 microdeletion and exposure to psychological stress during a critical period (postnatal days 30–40) in the development of impaired sensorimotor gating and psychostimulant drug sensitivity that are linked to psychosis (Giovanoli et al., 2019).

Efforts to develop a radiotracer for imaging the α7-nAChR *in vivo* with PET began in the early 2000s as reviewed in Horti (2015), but it proved challenging to identify a compound with high specific binding.

Since the concentration of the α7-nAChR in the brain is low (Bmax ≈ 6–16 fmol/mg protein) (Kulak et al., 2006; Marutle et al., 2001), the targeted binding affinity for candidate radiotracers is in the sub-nanomolar range (Horti, 2015). In 2013, chemists at Johns Hopkins University synthesized a series of candidate PET tracers (Gao et al., 2013), from which ASEM was selected (Horti et al., 2014) based on optimal *in vitro* binding affinity, target selectivity, and characteristics relevant to blood-brain barrier permeability (See (Horti, 2015)). Baboon studies with [$^{18}$F]ASEM PET showed dose-dependent blockade with SSR180711, a selective α7-nAChR partial agonist, and the estimated *in vivo* specific binding of [$^{18}$F]ASEM in the brain regions enriched with α7-nAChRs was 80%–90% (Horti et al., 2014). Recent studies using [$^{18}$F]ASEM PET in the human brain support its use to estimate regional availability of the α7-nAChR (Hillmer et al., 2017; Wong et al., 2014), and suggest that the availability of the receptor may change over healthy aging (Coughlin et al., 2018a)

In a cross-sectional, pilot [$^{18}$F]ASEM PET study of non-smoking individuals, young adults with recent-onset psychosis [non-affective psychosis or affective psychosis], and particularly those with non-affective psychosis, showed lower hippocampal binding of [$^{18}$F]ASEM than healthy controls after adjusting for age (Coughlin et al., 2018b) (Fig. 1A). Among all patients, lower [$^{18}$F]ASEM binding was associated with lower performance in two cognitive domains (processing speed, verbal memory) after adjusting for age. While the primary analyses focused on hippocampal binding [total distribution volume ($V_T$)] using PET data after partial volume correction, parametric images of $V_T$ derived from data without partial volume correction suggest that the α7-nAChR may be low in its availability across the brains of patients with recent-onset psychosis, particularly those with non-affective psychosis, compared to healthy controls (Fig. 1B). More work is needed since the patients were predominantly female and a few were treated with lithium or antipsychotic monotherapy at the time of scanning. The effects of clinical variables including psychotropic medication use on [$^{18}$F]ASEM binding need further evaluation. Nevertheless, we posit that those individuals with psychosis and low availability of the receptor relative to controls may prove more likely to benefit therapeutically from the emerging medications that augment the activity of the α7-nAChR. Results of larger studies of [$^{18}$F]ASEM PET in psychosis are needed first to validate the presence of this subgroup, and a cautious tone is to be taken in the setting of mixed benefits observed in recent clinical trials using full or partial α7-nAChR agonist medications (Tregellas and Wylie, 2018). On the other hand, there is more enthusiasm for pursuing positive allosteric modulators (PAMs) of the α7-nAChR, such as AVL-3288 (Gee et al., 2017), since PAMs preserve normal kinetics of receptor desensitization (type I PAM) or block desensitization (type 2 PAM). A PAM may therefore yield more favorable pharmacological response upon binding the α7-nAChR. In addition, study of the effect of augmented α7-nAChR activity on downstream DSC in associative striatum *in vivo* may elucidate further the contribution of α7-nAChR to dopaminergic disruption in some individuals with psychosis (see above).

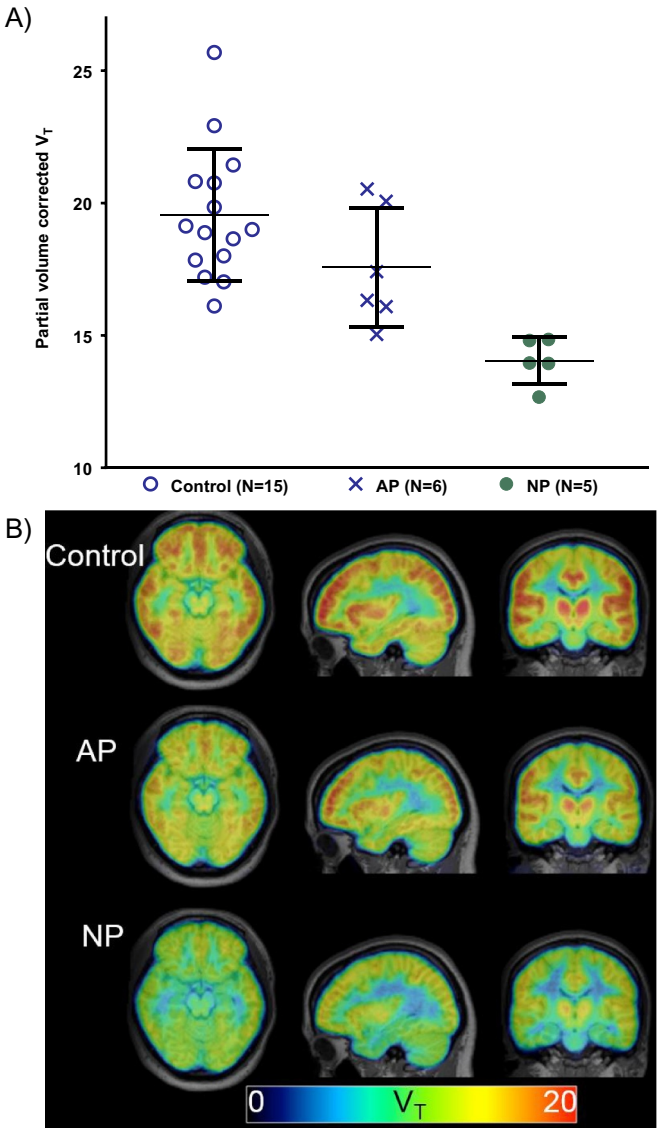


**Fig. 1.** Comparison between $^{18}$F-ASEM total distribution volume ($V_T$) values from non-smoking participants that were grouped as healthy controls ($N$ = 15), patients with recent-onset of affective psychosis (AP) ($N$ = 6) or patients with recent-onset of non-affective psychosis (NP) ($N$ = 5). A) Scatterplot of $^{18}$F-ASEM $V_T$ values in hippocampus from healthy controls, patients with AP and patients with NP. $V_T$ was estimated from images corrected for partial volume effects and mean and standard deviation values are shown (lines). B) Mean parametric $^{18}$F-ASEM $V_T$ images derived from PET data that were uncorrected for partial volume effects from the study population of 15 controls (top panel), six patients with AP (middle panel), and five patients with NP (lower panel) suggest group differences in binding outside the hippocampus as well. Images are displayed in groups of three views (left to right: axial, sagittal, coronal) and $V_T$ is in units of mL cm$^{-3}$. This research was originally published in JNM (Coughlin et al., 2018b).

## 4. Monitoring the role of microglia and response to neuroimmune therapies in psychosis using emerging radiotracers with PET

A better mechanistic understanding of the multifactorial etiologies of psychotic conditions will aid in the pursuit of stratifying patients. One area of continued scientific investigation is understanding the role of neuroimmunity in psychosis. Regardless of evidence refuting a primary pathogenic role of the neuroimmunity in schizophrenia (Birnbaum et al., 2018), intrinsic gene-environment interactions that contribute to psychosis can influence gene expression profiles of microglia, the resident immune cells in the brain. Resulting shifts in microglial phenotypes and responses (Gosselin et al., 2017) may shape the clinical phenomenology or the course of psychotic conditions.

Probing the neuroimmune response in psychosis has been limited in part by the inability to image microglia specifically in the human brain *in vivo*. Many studies have been conducted in clinical populations with schizophrenia using PET imaging of the translocator protein 18 kDa (TSPO), a protein on the outer mitochondrial membrane that is upregulated by activated microglia (Marques et al., 2018; Plaven-Sigray et al., 2018). However TSPO is expressed on several cell types other than microglia and its altered expression may reflect its roles in non-immune processes (cellular metabolism, oxidative stress) (Notter et al., 2018). For example, meta-analyses of cerebrospinal fluid (CSF) markers support elevated levels of the interleukin-6 (IL-6) and interleukin-8 in

individuals with schizophrenia (Gallego et al., 2018; Orlovska-Waast et al., 2018), but TSPO binding did not correlate with CSF IL-6 levels in individuals with recent onset of psychosis (Coughlin et al., 2016). In order to elucidate better the role of the neuroimmune response in psychosis, PET tracers targeting other biochemical markers relevant to neuroimmunity are needed (Notter et al., 2018).

Comprehensive review of non-TSPO, emerging targets for imaging the neuroimmune response with PET extends beyond our focus and we refer readers to recent excellent reviews (Janssen et al., 2018; Narayanaswami et al., 2018). Recently developed radiotracers to image the upregulation of cyclooxygenase (COX) 1 on activated microglia include [$^{11}$C]PS13 and [$^{18}$F]PS2 (Shrestha et al., 2018; Singh et al., 2018). [$^{11}$C]MC1 (Kim et al., 2018) targets COX 2 that is upregulated on microglia for potential neuroprotective effect (Aid et al., 2008). Low specific uptake in brains of healthy rhesus monkeys suggests that [$^{11}$C]MC1 PET is most promising for use in inflammatory conditions with robust upregulation of COX-2 (Kim et al., 2018). The pursuit of imaging methods that target molecules only expressed by microglia is ongoing. One candidate molecule is the colony stimulating factor 1 receptor (CSF1R, also known as c-FMS, CD-115, or M-CSFR), which is essentially restricted to expression by microglia in the human brain (Akiyama et al., 1994; Zhang et al., 2014). Imaging CSF1R (Horti et al., 2019) would facilitate testing for proliferation of microglia in the brains of a subset of individuals with psychosis. Radiotracers targeting microglia-specific phenotypes are also being pursued. For example, the P2Y12 receptor is expressed most prominently by microglia with anti-inflammatory M2 phenotype although radiotracer development for this target is challenging (Janssen et al., 2018).

It is in the context of the complexity and variability in neuroimmune responses that the field should not be dissuaded by the lack of benefit observed in the recent large, multi-center double-blind, randomized, placebo-controlled study of adjunctive minocycline in recent onset of schizophrenia. Minocycline is a neuroprotective medication that inhibits microglial activation, and results of the trial did not support a prominent role of activated microglia across this patient population nor of benefit from 12-month exposure to minocycline (Deakin et al., 2018). A second multi-center double-blind, parallel group, placebo-controlled study of add-on minocycline demonstrated similar lack of benefit in a population of chronically-ill individuals with schizophrenia (Weiser et al., 2018). However, it remains under debate whether there is a subgroup of individuals with psychosis and detrimental microglial signaling that may benefit from immunotherapy (Kishimoto et al., 2018; Mondelli et al., 2017; Pillinger et al., 2018). PET-based tools to measure specific cells and immune pathways related to the neuroimmune response non-invasively are needed to help test whether a subtype with pathological immune response exists among those with psychosis. If such a subtype is identified, PET data may guide the selection of participants for future clinical trials using immune-modulating therapies and PET could be used to monitor the neuroimmune response to treatment. The monitoring of neuroimmune markers during potent immunotherapy such as adjunctive monocloncal antibody therapy may prove advantageous in the assessment of adverse effects in the central nervous system (CNS) since strong immunosuppression is a risk factor for secondary infection, demyelinating disease, or malignancy (Miller and Buckley, 2016).

In parallel, PET study of neuroimmunity in psychotic conditions will benefit from the growing body of research focusing on the response of microglia to changes in the CNS microenvironment and in response to disturbed CNS homeostasis (Masgrau et al., 2017). As *in vitro* studies elucidate the signaling factors that regulate microglia phenotypes in health and disease, this knowledge can be applied to the study of microglia in complex culture systems to model gene-environment effects on microglia and their interplay with other cells (neurons, astrocytes) that are relevant to psychosis (Gosselin et al., 2017). Modeling the *in vivo* phenotype of microglia and interactions with other cell types using a CNS organoid model (Ormel et al., 2018) may prove most helpful in elucidating the hypothesized relationships between aberrant microglial response and dysfunction of pyramidal and inhibitory neurons in psychotic conditions (Volk, 2017). That knowledge can then guide future radiotracer development, small animal PET studies in relevant models, and PET neuroimaging in patients.

## 5. Moving forward using PET in the shift toward precision psychiatry

Above we highlight findings that suggest ways to stratify patients with psychosis from biochemical signatures found using PET. These examples suggest how PET data, if validated further, may inform treatment decisions using existing and emerging medications or provide means to monitoring therapeutic response toward improved patient outcomes. Individuals with new or recent onset of psychosis will benefit in particular from a method that identifies effective treatment efficiently since delay in optimal treatment often burdens affected young adults trying to succeed in school or employment. It also contributes to disengagement with care and non-adherence with future treatment. As the field continues forward toward precision psychiatry, it will be important to examine PET as a key tool to gather data relevant to precision approaches to care.

We acknowledge our optimistic tone in presenting early PET findings in the context of precision medicine. The Precision Medicine Initiative describes the movement into areas outside of cancer research as a long-term research goal (ghr.nlm.nih.gov/primer/precisionmedicine/initiative), and much work remains in assessing the benefit and cost-effectiveness of precision imaging tactics in psychiatry (Silbersweig and Rauch, 2017). The success of applying precision care to any patient population will depend on 1. Linking variation in treatment responses to key factors among individuals, 2. Methods to detect those relevant factors toward subtyping patients, and 3. Availability of alternative interventions suited best to each subgroup of patients (Colijn et al., 2017; Psaty et al., 2018). These assumptions should be kept in mind as PET is used to identify discriminating patterns of brain biomarkers between subgroups of individuals with psychosis. First, crucial to identifying relevant factors and/or biomarkers is an improved mechanistic understanding of psychotic conditions. The underlying and interrelated pathways that influence psychosis will be uncovered best by parallel study of both human neurobiological research and model systems. For example, some brain markers may be identified with PET because they impart vulnerability or resilience to the onset of psychosis, or emerge as its consequence, without necessarily proving useful in predicting prognosis or guiding treatment. Causality may be tested more readily in animal models. Strategies for clinical prediction modeling from scientific data are the focus of recent scientific discussions (Fusar-Poli et al., 2018) and must be carefully considered in future protocols that aim to assess the clinical value of subtyping patients based on PET findings. Second, from a methodological perspective, more radiotracers for use with PET will likely need to come on-line to probe new, specific biomarkers in the brain. The utility of some neurobiological signatures on PET may be influenced by a temporal variability, underscoring a need for longitudinal characterization of the relationship between each imaging marker and the clinical population or course. In parallel, the call for data sharing initiatives to support the expansion of precision medicine (Feero et al., 2018) will need to incorporate PET data acquired using consensus methods that are validated for each radiotracer. A working group was recently formed to establish guidelines for meaningful sharing of PET data (with associated blood data for modeling radiotracer pharmacokinetics in brain) (NRM Authors, 2018). Successful PET data sharing will also facilitate study of larger datasets that are a benefit since human PET research is often limited by cost and specialized labor associated with radiotracer development, brain PET acquisition, data processing/analysis, and regulatory oversight. New analytic approaches to combine neuroimaging data with other genetic, health record, psychosocial, and

radiomic data, and then to feed these data into systematic, clinical decision support tools as proposed in the METSY project (Frank et al., 2018) are also needed. Third, the identification of interventions best suited to specific patients will require buy-in from multiple entities within the dynamic health care system to repurpose old therapies or develop new treatment options for potentially small subgroups of individuals with psychosis (Wafi and Mirnezami, 2018). Precision approaches will likely go through multiple iterations of refinement as longitudinal health benefits are assessed and compared to traditional clinical practices within different care delivery systems.

Nevertheless, the emphasis on stratifying individuals with psychosis to guide more precise clinical decision making offers hope to those living with psychosis, their practitioners, and the global community. The findings above provide early promise that PET data, among other data types, may prove useful in the pursuit of identifying precision strategies to improve clinical outcomes for individuals with psychosis.

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## Conflicts of interest

The authors declare no conflicts of interest.

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