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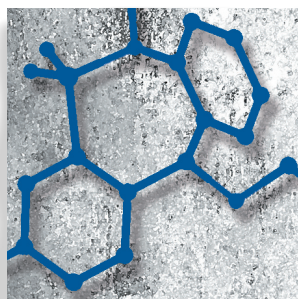
Molecular imaging as a guide for the treatment of central nervous system disorders

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Molecular imaging techniques have a number of advantages for research into the pathophysiology and treatment of central nervous system (CNS) disorders. Firstly, they provide a noninvasive means of characterizing physiological processes in the living brain, enabling molecular alterations to be linked to clinical changes. Secondly, the pathophysiological target in a given CNS disorder can be measured in animal models and in experimental human models in the same way, which enables translational research. Moreover, as molecular imaging facilitates the detection of functional change which precedes gross pathology, it is particularly useful for the early diagnosis and treatment of CNS disorders.

This review considers the application of molecular imaging to CNS disorders focusing on its potential to inform the development and evaluation of treatments. We focus on schizophrenia, Parkinson's disease, depression, and dementia as major CNS disorders. We also review the potential of molecular imaging to guide new drug development for CNS disorders.

Introduction

Molecular imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) enable the in vivo characterization and measurement of biologic processes using high-affinity and high-specificity molecular probes.[1] PET and SPECT use molecules labeled with a radionuclide that emits photons, known as a radiotracer or radioligand, that are detected in the scanner to provide data on the localization of the radiolabeled molecule in the tissue of interest. As such they provide a noninvasive means of visualizing, and characterizing physiological processes in vivo and the opportunity to make discoveries in the living, intact brain.

The major differences between PET and SPECT stem from the nature of the radionuclides used to label the tracer. The most commonly used radionuclides are ^{99m}Tc, ^{111}In, ^{123}I and ^{201}Tl for SPECT, and ^{11}C, ^{13}N, ^{15}O and ^{18}F for PET. The radionuclides used for SPECT have relatively long half-lives, in the range of hours, and emit a single photon. In contrast, those used in PET have shorter half-lives, in the range of minutes to just under 2 hours in the case of ^{18}F, and emit a positron, which annihilates when it collides with nearby electrons to emit two photons. The

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difference in the nature of photon emission leads to differences in emission detectors and image construction—SPECT uses collimation and PET uses coincidence detection. The advantages and limitations of both techniques follow from these properties—as SPECT tracers have longer half-lives they do not need an on-site cyclotron and, multiple scans are possible from one synthesis; this means they are cheaper to make than PET tracers. However, PET uses radionuclides that tend to be easily combined with biological molecules, and has better resolution.

Imaging in vivo can avoid the various potential biases or confounds of ex vivo studies, such as exposure to psychotropic drugs or mis-counting object fragments in a sectioned tissue volume[2] whilst also enabling molecular alterations to be linked to clinical changes. An attractive feature of molecular imaging is that the pathophysiological target in a given disorder can be measured in animal models and in experimental human models in the same way, which enables translational research bridging the laboratory to the clinic. Moreover, as molecular changes typically precede gross pathology, molecular imaging may enable early diagnosis and treatment of diseases.

Molecular imaging has provided a number of key insights into the pathophysiology and treatment of central nervous system (CNS) disorders such as schizophrenia, Parkinson's disease, depression, and dementia. This review considers the application of molecular imaging to CNS disorders, focusing on its potential to inform the development and evaluation of treatments. We focus on schizophrenia, Parkinson's disease, depression, and dementia as major CNS disorders where molecular imaging has provided a number of key insights. We also review the potential of molecular imaging to guide new drug development for CNS disorders. *Table I* summarizes the ways molecular imaging has advanced our understanding of CNS disorders, while *Table II* outlines its advantages and limitations.

Schizophrenia

Schizophrenia is a chronic, severe mental illness characterized by psychotic symptoms such as hallucinations and delusions often coupled with cognitive and social impairments. The discovery of the first antipsychotic drug, chlorpromazine, was the outcome of serendipity rather than rational drug design based on understanding

of pathophysiology.[3] It was subsequently discovered that chlorpromazine blocks dopamine receptors, and, despite varying widely in their affinity at other receptors, all antipsychotic drugs currently in the market block dopamine D_2 receptors[4] and their affinity for D_2 receptors closely parallels their clinical effectiveness.[5,6] Thus the discovery of antipsychotic drugs informed understanding of the pathophysiology of schizophrenia, by providing indirect evidence that dopamine dysfunction contributed to the disorder. The focus then was on $D_{2/3}$

Pathophysiology
- Identified that the locus of the largest dopaminergic abnormality in schizophrenia is presynaptic
- Patients with major depressive disorder shows altered 5-HT$_{1A}$ receptor density and elevated monoamine oxidase-A density
- Dopaminergic dysfunction correlates with symptom severity in Parkinson's disease
- Amyloid is elevated early in the overall Alzheimer's disease process

Treatment
- The optimum dosing for psychotropic drugs, for example antipsychotic dopamine receptor occupancy of 60% to 80% optimizes clinical response whilst minimizing the risk of parkinsonism in schizophrenia
- Determining that treatments under development cross the blood-brain barrier and act at the desired molecular target
- Identifying that selective serotonin uptake inhibitor treatment initially reduces brain serotonin, potentially explaining why antidepressant treatment takes several weeks for clinical response
- [^{18}F]FDG (fluro-2-deoxyglucose) and [^{18}F]DOPA positron emission tomography can be used for evaluating and monitoring the antiparkinsonian therapy
- [^{11}C]PIB (Pittsburgh compound B) can evaluate whether antiamyloid agents are able to reduce brain amyloid β load

Diagnosis
- Identified dopamine synthesis capacity as specific to high risk individuals who go on to psychosis, potentially enabling early diagnosis
- DaTscan using [^{123}I]ioflupane single photon emission computed tomography is licensed for the differentiation of essential tremor from Parkinson's disease
- [^{18}F]FDG and [^{11}C]PIB can be used for the early diagnosis of Alzheimer's disease
- [^{18}F]florbetapir has been approved as a diagnostic tool for Alzheimer's disease

Table I. How molecular imaging has advanced understanding of central nervous system disorders.

receptors, and postmortem studies suggested there was a large elevation in schizophrenia (see paper by Cross et al[7] and review by Howes and Kapur[8]). However, it was not until the application of molecular imaging to schizophrenia research that it became possible to test the dopamine hypothesis in the living brain and to investigate the locus of dopamine abnormalities in detail. Since then there have been more than fifty molecular imaging studies of the dopaminergic system in schizophrenia, beginning with seminal findings in the mid-1980s and 1990s.[9-15] These provide consistent and robust evidence for subcortical presynaptic dopamine abnormalities, specifically elevated dopamine synthesis and release capacity. A recent meta-analysis found the effect size for this was large—Cohen's d=0.8—whilst there was little if any alteration in $D_{2/3}$ receptors.[9] Molecular imaging has thus redefined understanding of the nature of dopaminergic dysfunction in schizophrenia by showing that the marked dopaminergic alterations in schizophrenia affect presynaptic function, and not $D_{2/3}$ receptor availability, as was initially thought. As many of the environmental risk factors for schizophrenia may converge to dysregulate presynaptic dopamine, it has been suggested that this is the final common pathway to psychosis.[8] This is supported by evidence that more of the variance in dopamine synthesis capacity is explained by environmental than heritable factors.[16] Imaging dopamine synthesis capacity has been shown to have high sensitivity and specificity for schizophrenia.[17] Furthermore, the studies to date indicate that patients with other common adult psychiatric disorders without psychosis, such as

Advantages
• Quantifies specific molecular targets down to sub-nanomolar levels
• Links biological processes to symptoms and other clinical outcomes
• Enables treatments to be evaluated and monitored
• Enable translational approaches
Limitations
• Practical implementation difficulties (eg, higher cost, on-site cyclotron)
• Exposure to ionizing radiation
• Requires team approaches (eg, psychiatrist, radiopharmacist, physicist)
• Limited to molecular targets for which good radiotracers can be developed

Table II. Advantages and limitations of molecular imaging.

depression or bipolar disorder, do not show elevated dopamine synthesis capacity (see review by Howes et al[18]). Elevated dopamine synthesis capacity is also not seen in healthy twin siblings of patients with schizophrenia,[19] or in people with long-term subclinical psychotic symptoms who have not developed schizophrenia despite many years of symptoms,[20] further suggesting specificity for the clinical disorder rather than a trait phenomenon. Although this requires further evaluation, these findings suggests that molecular imaging of dopamine synthesis capacity may be clinically useful where there is diagnostic uncertainty such as early in the course of the illness. The importance of presynaptic dopaminergic dysfunction in schizophrenia is also supported by findings that elevated dopamine synthesis capacity predates the conversion to psychosis, and increases with the onset of psychosis.[21-24] Elevated dopamine synthesis capacity thus has potential as a biomarker for high risk of psychosis.

Findings of reduced frontal blood flow,[25-28] altered cortical structure[29,30] and the different distribution of dopamine receptors (ie, high density of D_1 in cortex and D_2 in subcortex) led to the reconceptualization of the dopamine hypothesis in 1980s to include regional specificity, which was first discussed by Bannon and Roth in 1983[31] and later by Andreasen in 1988.[32] Drawing on these and other findings, Davis et al[33] hypothesized that positive symptoms resulted from subcortical hyperdopaminergia and negative symptoms resulted from frontal hypodopaminergia. The relatively low density of dopamine neurons and receptors in cortical regions means that cortical dopaminergic function has proven harder to image than subcortical changes, and has only become possible in the last decade with the development of high-affinity tracers. Consequently, in contrast to the wealth of evidence for subcortical hyperdopaminergia, there have been relatively few studies of cortical dopaminergic function in schizophrenia, and, although meta-analysis suggests there are reductions in $D_{2/3}$ receptors, the effect is not marked (unpublished data). Nevertheless, recent evidence indicates that subcortical hyperdopaminergia is linked to cortical dysfunction, at least in the development of the disorder (see ref 21, and review in ref 34).

The molecular imaging findings of subcortical presynaptic dopamine dysfunction indicate that by blocking postsynaptic D_2 receptors, current antipsychotic drugs act to attenuate the effect of elevated dopamine release. However, though blockade of D_2 receptors helps relieve

the symptoms of schizophrenia, it does not correct the presynaptic dopamine abnormality and may even paradoxically worsen it in the short term. This is supported by several lines of evidence. Firstly, acute antipsychotic treatment in healthy volunteers increases dopamine synthesis capacity.[35] Secondly, although subchronic treatment is associated with a reduction, dopamine synthesis capacity nevertheless is elevated in patients even after long-term antipsychotic treatment.[36,37] Thus, given that the presynaptic abnormality is present despite long-term treatment, it is not surprising that patients relapse rapidly when antipsychotic drugs are stopped and there is nothing to block the consequence of the presynaptic dopamine dysregulation.

Whilst it has been known for some time that antipsychotic drugs block dopamine receptors,[38] molecular imaging was able to show that the dopamine D_2 receptor occupancy by antipsychotic drugs was significantly associated with clinical response to treatment.[39,40] These studies also demonstrated that there was therapeutic window for D_2 occupancy of between about 60% to 80%—with occupancy below 60% associated with little likelihood of response, whilst occupancy above 80% was associated with little added therapeutic benefit and a higher risk of side effects. However, a number of the second-generation antipsychotic drugs developed in the 1990s showed significantly higher affinity for $5\text{-}HT_{2A}$ receptors over D_2 receptors. Consequently focus shifted in the 1990s from dopamine to serotonin receptors, and particularly $5\text{-}HT_{2A}$ receptors, where antagonism was thought to provide improved efficacy and tolerability.[39,42-45] However, here molecular imaging studies have shown that antipsychotic efficacy is not associated with $5\text{-}HT_{2A}$ occupancy by antipsychotic drugs,[46] and that even in the newer drugs D_2 receptor occupancy is still necessary for antipsychotic response.[46] The evidence for presynaptic dopamine dysregulation in schizophrenia suggests that therapeutic advancement in schizophrenia requires targeting upstream regulation of dopamine, rather than D_2 receptors.[9] There has been considerable effort in this area to develop glutamatergic drugs. Dopamine and glutamate are comodulatory.[47] It has been suggested that dopaminergic dysregulation may result from upstream glutamatergic abnormalities[48-50] and that the glutamatergic abnormalities may, in turn, be worsened by the dopaminergic dysfunction.[50] Hypofunction of N-methyl-D-aspartate (NMDA) receptors is thought to result in increased release of glutamate via disinhibition of γ-aminobutyric acid (GABA)ergic interneuron[51] and

downstream dysregulation of dopamine neurons.[52-55] One promising glutamatergic target for treating schizophrenia is the glycine transporter, and a number of inhibitors are currently being evaluated. Glycine and glutamate are co-agonists for NMDA receptors.[56] Increasing synaptic glycine levels by glycine transporter inhibition is a potential strategy to improve NMDA receptor function without the risk of neurotoxic effects from the direct glutamatergic excitation of NMDA receptors.[57] Indeed, the endogenous glycine transporter inhibitor sarcosine has been found to show efficacy in reducing negative, cognitive, and positive symptoms of schizophrenia[58,59] and other glycine transporter inhibitor with higher affinity currently under development show promise in preclinical tests.[60] Another approach is to target type 2/3 metabotropic glutamate ($mGluR_{2/3}$) receptors. These are located in perisynaptic areas and provide negative feedback on glutamate release, protecting neurons from excessive glutamate transmission.[61] The $mGluR_{2/3}$ receptor agonist LY404039 (administered as the prodrug LY2140023) produced a promising result in the first trial, showing a marked reduction in positive, negative, and general symptom scores,[62] though subsequent clinical trials have not been positive[63] and this drug is no longer in the pipeline.[64] Activation of type 5 metabotropic glutamate receptors, functionally coupled with NMDA receptors, thereby improving the function of NMDA receptors, has also been suggested as an antipsychotic strategy.[65-67]

Whilst there are promising developments, the example of LY2140023 indicates that there are considerable challenges in developing new and better treatments for schizophrenia. Currently we know little about the nature of glutamatergic abnormalities in vivo in schizophrenia. Clearly understanding these and their impact on the dopamine system would greatly facilitate the development of drugs that specifically target key regulatory elements. The availability of novel tracers for imaging receptor subtypes and molecular processes in the brain, such as [11C]CMGDE,[68] [11C]ABP688,[69] and [11C]RO5013853[70] for imaging type 2/3 and type 5 metabotropic glutamate receptors, and glycine transporter respectively, has the potential to play a critical role here. However, molecular imaging has also identified another major potential reason for the difficulties in developing better treatment for schizophrenia—that is heterogeneity in the neurobiology of the disorder. For example, patients refractory to antipsychotic drugs do not exhibit the elevation in dopamine synthesis capacity,[37] which may suggest a different underlying pathophysiology prompting the devel-

opment of antipsychotic drugs with different mechanisms. Currently clinical trials recruit patients on the basis of the clinical presentation and not the underlying neurobiology. However, it is unlikely that one drug could successfully treat patients with different neurobiology. Patient stratification by underlying neurobiology based on a molecular imaging measure, for example, could be used to identify a homogenous group of patients to enter the trial. Identifying an efficacious drug is not the end of the story of course. It is then necessary to determine the best dosing strategy. In the past this was based on plasma kinetics, but it has become clear that there can be a marked disconnection between plasma levels and levels at the effector site in the brain.[71,72] Here molecular imaging has proven useful in providing information on the brain kinetics of candidate antipsychotic drugs to optimize study design and ultimately inform clinical dosing schedules.[71,73]

Depression

Major depressive disorder (MDD) is a common disorder, affecting approximately 15% to 20% of the population at some point in life.[74] It is characterized by affective, cognitive, and biological symptoms, and results in substantial personal suffering, as well as socioeconomic burden.[75,76] As in the case of schizophrenia, the development of pharmacological treatments has informed understanding of the biology of major depression. With the discovery that imipramine, an inhibitor of norepinephrine and other monoamine transmitters, improves depressive symptoms, the norepinephrine hypothesis of depression was formed, which posits that a deficiency in norepinephrine contributes to depression (for review, see Dell'Osso et al[37]). The next theory to gain favor, with the widespread use of antidepressant medication selectively targeting serotonin, was the serotonin hypothesis, which attributes the dysfunction of the serotonin system to depressive symptoms.[77] Further support for this has come from genetic studies that serotonin transporter (5-HTT) polymorphisms is the risk for MDD.[78] Molecular imaging studies have contributed to testing the monoamine hypotheses of MDD by measuring the baseline level of monoamine receptors, and transporters in patients and controls. A number of PET studies have investigated 5-HT$_{1A}$ receptors, which are thought to play a key role in maintaining stable serotonin transmission and to be involved in the mechanism of antidepressant

treatment. Most of these have shown that patients with MDD have reduced 5-HT$_{1A}$ receptor density, particularly in the raphe nucleus.[79-82] However, increased 5-HT$_{1A}$ receptor density has also been reported.[83] This apparent discrepancy may be due to methodological differences, particularly whether the 5-HT$_{1A}$ binding potential is determined using an arterial input function, which is considered the gold standard, or using a reference region.[84] In support of this methodological difference underlying the discrepancy, the group that has found increased 5-HT$_{1A}$ receptor density in MDD using the arterial input function, report reductions when they reanalyze their data using the reference region approach.[83,85] The 5-HT$_{1B}$ receptor is another presynaptic autoreceptor which inhibits serotonin and other monoamine neurotransmitter release. A 20% decrease in 5-HT$_{1B}$ binding potential in the ventral striatum and pallidum of patients with depression has been reported, suggesting there may be abnormalities in other autoreceptors in MDD as well.[86] 5-HTT has also been a focus of investigation in MDD, particularly because of the importance of serotonin transporter inhibitors in the treatment of MDD. The development of radiotracers such as [^{11}C]DASB that have a high ratio of specific binding to serotonin transporters relative to nonspecific binding has facilitated research into serotonin transporter function in MDD. Though there are some conflicting results,[87-89] the majority of neuroreceptor imaging studies with [^{11}C]DASB have found decreased 5-HTT binding in patients with MDD.[90-93] This is supported by a recent meta-analysis that found a reduction in serotonin transporter availability in MDD with a medium effect size (unpublished data). The finding that depressed suicide attempters had lower 5-HTT binding compared with depressed nonattempters and control subjects[94] suggests that 5-HTT reductions are greater in patients with more severe illness. PET studies have also found evidence for alterations affecting one of the enzymes that break down monoamines. Specifically the density of monoamine oxidase-A (MAO-A) has been found to be elevated in MDD,[95,96] suggesting that the metabolism of monoamines is increased in MDD. Based on this, Meyer et al[95] hypothesized that the increased density of MAO-A in depression is the primary driver of reduced monoaminergic signal transduction in MDD. This suggests that dopaminergic and norepinephrinergic systems will be affected as well. There is some evidence on the dopaminergic system in MDD, showing slight decreases or no change in D$_1$ and D$_2$ receptor den-

sity, and a decrease in dopamine transporter binding.[97-99] However, the paucity of radiotracers for the norepinephrine system has limited investigation of this system in MDD, though some tracers for imaging norepinephrine transporter[100,101] and adrenergic receptors[102] are under development.

A major limit on understanding the role of serotonin in MDD has been that it has not been possible to index changes in serotonin levels in the brain. There is, however, emerging evidence that some serotonin receptor tracers are sensitive to changes in serotonin levels,[103-105] which promises to provide a means of testing this crucial aspect of serotonergic function.

The most widely used pharmacological treatments for depression are the selective serotonin reuptake inhibitors (SSRIs). Evaluation of 5-HTT binding of radiotracers with therapeutic doses of SSRIs shows an occupancy ranging from 65% to 87%.[106] In contrast to the case of antipsychotic drugs, the relationship between the occupancy and response still remain undefined and the clinical efficacy does not seem to correspond to dose increases. An apparent paradox for many years has been the observation that whilst SSRIs rapidly produce high levels of serotonin transporter blockade, the clinical response typically takes several weeks. However, a recent PET imaging study provides evidence that the initial action of SSRIs is an acute reduction in serotonin levels in terminal fields,[105] in line with preclinical studies which have shown that the initial effect of SSRIs is to reduce firing in the raphe nucleus and serotonin levels in the terminal fields.[107-113] In preclinical studies this acute effect resolves over the next few weeks of treatment as the raphe desensitizes.[113] Thus, the reduction in serotonin in terminal regions seen with acute citalopram in the human study could explain why SSRIs take some days to work, even worsening some symptoms initially. Non-monoaminergic targets have also received increasing attention in developing drugs for MDD.[114] New antidepressant developments have targeted acetylcholine receptors (spurred on by muscarinic and nicotinic antagonists showing antidepressant effects) and glutamate receptors (due to rapid antidepressant effects of ketamine, an NMDA receptor antagonist).[114,115] The development of radiotracer for these non-monoaminergic targets should help identify the best targets for drug development, as well as elucidation of the mechanism behind the slow onset of action of available antidepressants versus the rapid onset of action hoped for by the novel drugs.[99]

Parkinson's disease

Parkinson's disease (PD) is characterized by motor dysfunction such as resting tremor, bradykinesia, and rigidity, and also by non-motor symptoms such as depression, fatigue, and cognitive impairments. It is the second most common neurodegenerative disorder after Alzheimer's disease.[116] At post mortem, degeneration of dopaminergic neurons in mesostriatal pathways and deposits of a protein, alpha-synuclein, are typically seen. However, whilst this tells us about the end stage of the PD, molecular imaging of the dopaminergic system has been critical in determining the development and progression of PD pathophysiology.

Dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) are expressed in the terminals of dopaminergic neurons and radioligand binding to these targets is an indicator of the integrity of nigrostriatal projections. Lower uptake of these tracers is correlated with greater symptom severity in PD, providing evidence linking loss of terminals with the clinical expression of the disorder.[117] Similarly, lower [18F]DOPA uptake in the putamen has also been correlated with greater severity of motor symptoms and greater severity of bradykinesia and rigidity.[118,119] Furthermore, several studies have demonstrated the striatal [18F]DOPA uptake declines more rapidly in PD than in age-matched controls, indicating the progression of pathophysiology.[120,121] [18F]DOPA PET imaging has shown that the decline in dopamine function starts in the dorsal caudate and putamen contralateral to the side with dominant motor symptoms.[122] Furthermore, the rate of decline is greater in the putamen than in caudate, suggesting that the progression of dopaminergic hypofunction in the putamen is faster in the beginning of the disease.[123] Molecular imaging has also revealed abnormalities in the serotonergic system in PD patients.[124,125] In particular, reduced 5-HT$_{1A}$ receptor density[125] and reduced serotonin transporter availability[126,128] have been found in the raphe nucleus in PD. These findings have been important in indicating that other midbrain nuclei are involved in the pathophysiology of PD, and linking abnormalities in serotoninergic function to some of the non-motor aspects of PD, such as fatigue and depression.[124,127] Cognitive deficits are a major problem in PD. Here molecular imaging has linked these to altered dopaminergic and cholinergic function. For example, reduced [18F]DOPA uptake in the striatum has been correlated with impaired visual memory and verbal

memory.[128,129] Whilst this may reflect the impact of altered striatal dopaminergic function on cognition, there is also evidence for widespread reductions in cortical metabolism in PD.[130] Furthermore, longitudinal imaging of PD patients has shown that PD patients initially without dementia who later developed dementia (PDD) showed decreases in metabolism over time in the occipital cortex, posterior cingulate cortex, and caudate nucleus, whereas PD patients not diagnosed with dementia at follow-up showed only mild reductions over time in the primary occipital cortex.[131] Thus functional changes in both cortical and subcortical structures are associated with the development of cognitive impairments and dementia in PD. These findings indicate that PD is a multisystem neurodegenerative disorder, showing cholinergic and serotoninergic changes as well as pronounced nigrostriatal denervation.[132,133]

There are a number of similar neurodegenerative conditions, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration, dementia with Lewy bodies, vascular parkinsonism, and essential tremor, which have different prognoses and treatments. A major challenge in the management of PD is thus making an early and accurate diagnosis. A search for biomarkers to help differentiate PD from other neurodegenerative diseases has yielded a few promising results, and one, DaTscan, has received FDA approval and is available commercially. DaTscan uses [123I]ioflupane SPECT to evaluate parkinsonian symptoms and is able to distinguish PD from essential tremor with a sensitivity and specificity of 95% and 93% respectively.[134] Early PD can be difficult to distinguish from essential tremor, but treatment is generally only indicated in PD. This DaTscan can be particularly useful to identify early PD, and avoid inappropriate treatment for essential tremor. Though DaTscan is licensed only for the differentiation of essential tremor from PD, there has been much discussion on its use for the differentiation of other parkinsonian syndromes such as MSA and PSP from PD.[135] Other molecular imaging biomarker candidates to distinguish PD from other parkinsonian syndromes such as MSA include [11C]raclopride and [18F]FDG PET.[136] Reduction of [11C]raclopride binding potential and [18F]FDG uptake in the putamen accurately discriminated MSA from PD.[136] [18F]FDG uptake alone can be useful in the differential diagnosis of parkinsonian syndromes. The patients with PD show a significant glucose hypometabolism in the prefrontal, lateral frontal, and

parietal cortices, and the cingulate and caudate areas,[137,138] whilst MSA patients exhibited decreased metabolism in the putamen, pons and cerebellum.[139]

Levodopa, a dopamine precursor, has been used as the main treatment for PD since the 1960s. Along with levodopa, other enhancers of dopaminergic transmission are widely used. These include drugs that inhibit the break-down of dopamine such as monoamine oxidase B inhibitors selegiline, rasagiline, and deprenyl; and the catechol-O-methyltransferase inhibitors entacapone and tolcapone; and dopamine receptor agonists such as bromocriptine, pramipexole, apomorphine, and ropinirole. Drugs that act on related systems such as amantadine and the antimuscarinic agents benztropine, trihexyphenidyl, procyclidine, and biperiden, also have a role, although primarily as adjunctive agents.[140] Deep brain stimulation (DBS), an implantation of a stimulatory electrode directly into certain areas of the brain, has been successful in managing PD symptoms.[141] Whilst these treatments provide symptomatic relief, transplantation of dopaminergic cell to substitute for the lost midbrain dopamine neuron could potentially reverse the pathophysiological changes, and initial trial results have been promising.[142] Molecular imaging has been used to evaluate PD treatment. For example, reductions in [11C]raclopride binding in the putamen correlate with improvements in rigidity and bradykinesia, as well as the occurrence of dyskinesia after the treatment with levodopa.[143] [18F]FDG PET has also been used to assess the effect of cholinergic agents in PD with dementia, showing that donepezil treatment increases cerebral metabolism in the left angular gyrus and in the right superior and left middle orbitofrontal gyri.[144] Molecular imaging may also be used to inform the prognosis and response to treatment (so called "theragnostics"). For example, PD patients who initially fulfilled the PD diagnostic criteria with normal dopamine transporter scans show a good prognosis and can have their antiparkinsonian therapy withdrawn without clinical deterioration.[145] Such cases may be an example of nondegenerative form of parkinsonism.

There are a number of difficulties when attempting to assess the progression of PD using clinical scales as these are mostly subjective, nonlinear scales and often biased toward specific symptoms.[146] In addition, symptomatic therapy for PD effectively masks the symptoms for the assessment of disease progression.[147] Here molecular imaging provides an objective measure of the underlying

Pharmacology

pathophysiology that can be used to evaluate progression. In particular striatal [18F]DOPA uptake has been shown to correlate with dopaminergic cell densities in the substantia nigra and with striatal dopamine levels of patients.[148] Furthermore, [18F]DOPA PET imaging is also highly reliable[149] and appears to be uninfluenced by dopaminergic medication,[150,151] suggesting the usefulness of [18F]DOPA PET as a biomarker for monitoring the progression. As well as providing a means to monitor disease progression and the effect of treatment, molecular imaging can be useful to examine the efficacy of restorative approaches to PD. A recent long-term study of cell implantation in PD reported that post-transplantation increases in [18F]DOPA uptake were related to subsequent clinical outcome, suggesting it could be used to monitor the success of transplantation.[152]

Dementia

Dementias are neurodegenerative disorders characterized by progressive cognitive decline and functional impairments. The most common forms of dementia are Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies (DLB), and frontotemporal lobar dementia (FTLD).[153] The pathoetiology of Alzheimer's disease has been extensively studied. Hallmarks of AD are abnormally high amyloid beta (Aβ) and tau protein deposits in the brain, cerebral atrophy, and reduced cholinergic function, although definite diagnosis of AD needs postmortem pathologic confirmation. Accordingly, one process in AD pathophysiology is the accumulation of β amyloid (40 a.a. and 42 a.a. isoforms) through cleavage of amyloid precursor protein by beta and gamma secretase, while another is the hyperphosphorylation of the tau protein that results in its aggregation intracellularly. Mild cognitive impairment (MCI) preceding dementia can be accompanied by many changes underlying AD, and such cases are at a higher risk of progressing to AD.[154] DLB is characterized by proteinaceous deposits (made up of α synuclein) throughout the brain, and by the degeneration of cholinergic and dopaminergic neurons.

PET has been useful in the early diagnosis of AD, and in the differential diagnosis of different kinds of dementia. Abnormalities in regional cerebral glucose metabolism, as measured by [18F]FDG, have been shown in AD, with predominant reductions in glucose metabolism in temporoparietal regions, precuneus, posterior cingulate cortex and frontal cortex.[155,156] However, more recent attention has focused on imaging amyoid plaques. The most extensively used and validated tracer for Aβ plaques is N-methyl-[11C]2-(4-methylaminophenyl)-6-hydroxybenzothiazole, also known as Pittsburgh Compound B (PIB). Higher binding potentials of [11C]PIB are seen in the prefrontal cortex, precuneus, and posterior cingulate of AD patients in comparison with controls.[157] β-Amyloid deposition seems to be most active during the early phase of the disease, plateauing thereafter.[158] Cognitive impairment does not seem to correlate with the extent of [11C]PIB binding, further supporting the claim that Aβ deposits are restricted to early stages of AD.[159] The poor correlation between [11C]PIB binding and cognitive impairment has suggested that this imaging test must be interpreted with caution and has raised questions about the role of Aβ protein as a contributor to the overall disease process. Nevertheless, [11C]PIB PET imaging appears to be able to detect prodromal AD earlier and to better distinguish between MCI subtypes than [18F]FDG PET.[160] However, metabolic abnormalities in the brain closely parallel cognitive deficits, and share a more regionally specified distribution compared with β-amyloid deposits.[161]

Although PIB has proven very informative for studying AD, the short half-life of carbon-11 limits its clinical application to centres with an on-site cyclotron. Consequently considerable effort has gone into developing fluorinated tracers for amyloid plaques and this has resulted in [18F]flutemetamol, [18F]florbetapir, [18F]florbetaben, and other fluorinated equivalents of [11C]PIB[157] being developed. One of these, [18F]florbetapir (AMYViD™, Eli Lilly), has recently been approved by the FDA for PET imaging of β-amyloid neuritic plaques in the living brain. The sensitivity of [18F]florbetapir scans for the detection of β-amyloid neuritic plaques was 92% (range, 69 to 95) and the specificity was 95% (range, 90 to 100).[162] Accurate and reliable estimation of the density of β amyloid neuritic plaques by [18F]florbetapir was verified through clinical and nonclinical studies and it is expected to provide prognostic and predictive information in AD.[162]

Molecular imaging has enabled the investigation of other aspects of the pathophysiological process in AD, such as neuroinflammation. The PET tracer [11C]PK11195 provides a measure of the activation of microglia in the brain, reflecting neuroinflammation. Studies have found elevated [11C]PK11195 binding in the temporoparietal, cingulate, and entorhinal cortex in

AD,[163] which was also correlated with impairments in cognitive performance.[164] Activation of astrocytes, as imaged with [^{11}C]DED, has also been shown to be increased in AD and mild cognitive impairment (MCI),[165] which is a syndrome defined as cognitive decline greater than expected for an individual's age and education level that can be a precursor to AD.[166] Moreover, MCI demonstrated higher [^{11}C]DED binding than AD suggesting the activation of astrocyte could be an early dynamic phenomenon in the time course of AD.[165] As such, each tracer has its advantages and their combined use is expected to detect the earliest AD pathogenic events, improve classification and monitor progression.[167] The Alzheimer's Disease Neuroimaging Initiative (ADNI), a global research effort, has endeavored to validate such biomarkers for the early detection and tracking of AD. ADNI has developed standardized methods for clinical, MRI and PET and cerebrospinal fluid (CSF) biomarkers in a multicenter setting[168] and found that combining MRI, [^{18}F]FDG PET, and CSF data with routine clinical tests significantly increased the accuracy of predicting conversion to AD compared with clinical testing alone,[169] decreasing the misclassification rate from 41.3% to 28.4%. [^{18}F]FDG PET contributed more to the improvement in the accuracy than CSF or MRI, showing the usefulness of molecular imaging in the early diagnosis of AD.[169]

Current drugs for AD include acetylcholinerase inhibitors such as donepezil and rivastigmine; memantine, a drug that blocks NMDA receptors,[170] and drugs that combat the neurotoxic effect of Aβ plaques including the L-type calcium channel antagonist nimopidine, and antioxidants such as vitamin E.[171] Candidate drugs for AD include beta and gamma secretase inhibitors, and immunogenic synthetic Aβ42 or monoclonal antibodies (eg, bapineuzumab) against Aβ42.[172] Molecular imaging is not only useful for the early detection of AD and MCI, but also for predicting treatment response to anti-amyloid and other drugs, and may serve as a surrogate outcome measure.[172,173] For example, some PET studies reported reduction of brain Aβ plaques measured by [^{11}C]PIB after the treatment with anti-amyloid agents, though the disease modifying effects need further confirmation.[174-176] The imaging of inflammatory mediators such as microglia may help assess the effectiveness of drugs that are targeted toward reducing inflammation in the brain, such as NSAIDs. Moreover, since abnormalities in cholinergic, noradrenergic, serotonergic, and dopaminergic systems are all thought to contribute to AD pathophysiology, imaging of these neurotransmitter systems will help develop further drug targets and evaluate their efficacy.[173]

Conclusions

How molecular imaging has uniquely changed thinking about these illnesses

Molecular imaging enables molecular processes to be related to the clinical presentation, and subsequent course of CNS disorders. For example, in the case of schizophrenia it has provided data on the regional nature of the dopamine alterations in the brain at the onset, and even predating the illness. Furthermore, molecular imaging has narrowed down the nature of the dopaminergic alterations at onset of the disorder- identifying that the major alterations are presynaptic and not at the receptor or transporter level- and related this to subsequent clinical outcomes. This has enabled the dopamine hypothesis of schizophrenia to be revised in ways that would not have been possible with other techniques. Molecular imaging also clarified how antipsychotics work—demonstrating that $D_{2/3}$, but not D_1 or 5-HT$_{2A}$, receptor occupancy is linked to subsequent treatment response and side effects. This finding has contributed to a change in clinical practice away from the use of high dose antipsychotics towards lower doses. These studies also identified that atypical antipsychotics also engage the same $D_{2/3}$ mechanism as the typical ones.

Whilst CNS disorders are currently largely diagnosed based on their clinical presentation, they show heterogeneous clinical courses and response to the treatment. Here molecular imaging has begun to provide evidence of different molecular pathologies within the same syndrome, potentially explaining some of the heterogeneity in CNS disorders. This has clear translational potential in schizophrenia where the finding that there are "dopaminergic" and "nondopaminergic" subtypes suggests the latter group could be identified for emerging alternatives to the dopamine blocking drugs that are currently available. The use of DaTscan for differentiation of parkinsonian syndromes has already made it to the clinic. Furthermore, as shown in schizophrenia and dementia, molecular imaging is beginning to be applied to identify high-risk groups prior to the onset of the frank disorder. There is thus the potential to intervene

Pharmacology

early, before disability has progressed, to prevent the onset of disorder.

How molecular imaging can be applied for the development of new treatments

Molecular imaging has the potential to inform drug discovery in a number of ways. Firstly, it enables specific drug targets to be identified during the development and progression of a disorder. In schizophrenia, for example, molecular imaging has determined that current drug treatments act downstream of the major dopaminergic abnormality, and has identified the presynaptic regulation of dopaminergic function as a key new target for drugs, whilst in AD the identification of neuroinflammation early in the disease has contributed to the development of anti-inflammatory treatments for the disease. Secondly, molecular imaging provides biomarkers to monitor treatments and provide pathophysiologically relevant end points to evaluate new therapies, as illustrated by the use of [18F]DOPA to monitor stem cell transplants in PD and [11C]PIB to assess the efficacy of antiplaque agents in AD. Thirdly, it identifies endophenotypes to stratify patients with a given disorder on the basis of their underlying neurobiology. Such neurobiol[g]cally defined endophenotypes will trigger significant paradigm shifts in new drug development for CNS disorders, from the past empirical approach based on trying treatments in heterogenous patient samples to targeting treatments to patients with a homogenous pathophysiology. Finally, the identification of molecular imaging biomarkers in a number of CNS disorders means it is possible to predict the efficacy of new treatments in animal models by measuring biomarkers, and to design clinical trials in an efficient way by subject stratification based on the endophenotypes. ❏

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La imaginología molecular como guía para el tratamiento de los trastornos del sistema nervioso central

Las técnicas de imaginología molecular tienen numerosas ventajas para la investigación acerca de la fisiopatología y el tratamiento de los trastornos del sistema nervioso central (SNC). Primero, porque ellas aportan formas no invasoras para la caracterización de procesos fisiológicos en el cerebro vivo, permitiendo que las alteraciones moleculares se relacionen con cambios clínicos. Segundo, porque el blanco fisiopatológico de un determinado trastorno del SNC puede ser medido de la misma forma en modelos animales y en modelos humanos experimentales, lo que permite la investigación translacional. Sin embargo, como la imaginología molecular facilita la detección del cambio funcional que precede a la patología grave, resulta especialmente útil para el diagnóstico y tratamiento precoces de los trastornos del SNC. Esta revisión examina la aplicación de la imaginología molecular en los trastornos del SNC y se enfoca en su potencial para informar sobre el desarrollo y evaluación de los tratamientos.

Este artículo centra la atención en esquizofrenia, Enfermedad de Parkinson, depresión y demencia como los principales trastornos del SNC. También se revisa el potencial de la imaginología molecular como guía para el desarrollo de nuevos fármacos para trastornos del SNC.

L'imagerie moléculaire : un guide pour le traitement des troubles du système nerveux central

Les avantages des techniques d'imagerie moléculaire sont nombreux pour la recherche physiopathologique et le traitement des troubles du SNC (système nerveux central). Elles permettent tout d'abord d'explorer de façon non invasive les processus physiologiques du cerveau vivant en liant les changements moléculaires aux modifications cliniques. Deuxièmement, une recherche translationnelle est rendue possible mesurant de la même façon dans un trouble donné du SNC, la cible physiopathologique dans des modèles animaux et dans des modèles humains expérimentaux. De plus, l'imagerie moléculaire permet la détection de modifications fonctionnelles précédant la pathologie manifeste, ce qui est particulièrement utile pour le diagnostic précoce et le traitement des troubles du SNC.

Dans cet article, nous nous intéressons à la capacité de l'imagerie moléculaire d'informer sur le développement et l'évaluation des traitements dans son application aux troubles du SNC, en particulier pour la schizophrénie, la maladie de Parkinson, la dépression et la démence, troubles majeurs du SNC. Nous analysons également la possibilité de piloter le développement de nouveaux médicaments des troubles du SNC par l'imagerie moléculaire.

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