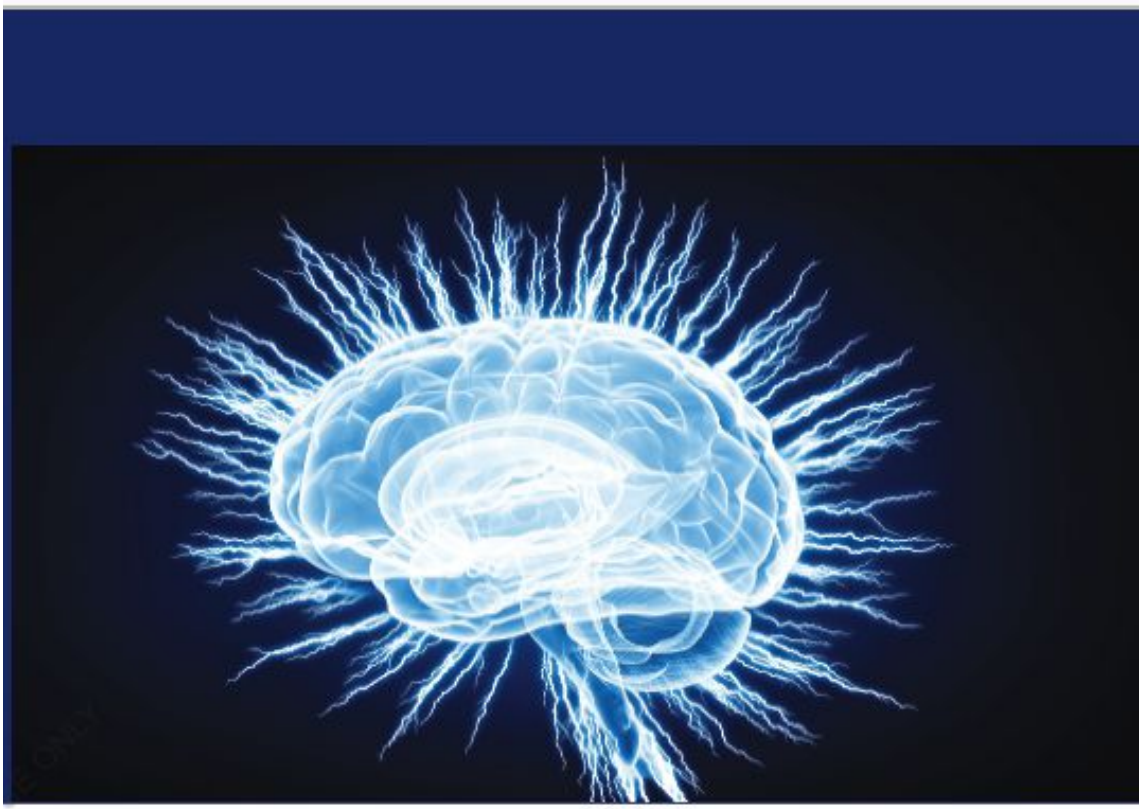

Bertil R.R. Perssom

A Story about Schizophrenia Imaging and Metabolism

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Schizophrenia Imaging and Metabolism

The author was already in the 1970s involved in Nuclear medicine imaging in Lund where David Ingvar and Göran Franzén studied the brain's regional blood flow in Schizophrenia patients. The introduction of magnetic resonance imaging MRI in the 1980th offered new methods for imaging CSF flow dynamics in the aqueduct. Functional fMRI may be another useful tool for defining the syndrome of Schizophrenia. Diffusion tensor imaging DTI and its combination with magnetic transfer imaging MTI indicate neuroinflammation in Schizophrenia.MR spectroscopy provides reliable quantification of more than fifteen different brain metabolites such as N-Acetyl Aspartic acid (NAA), Creatine, GABA, Glutamate, and Glutamine in various brain regions. Activation of the Tryptophan metabolism (TRYCAT) pathway appears to be involved in the development and pathophysiology of Schizophrenia. The dysfunction of the effect of the α-7nicotinic-acetyl-choline receptor (α7nAChR) and/or the N-methyl-D-Aspartate receptor (NMDAR). seems to contribute to cognitive impairment in Schizophrenia motivating new therapeutic strategies The final chapter reviews serum biomarkers.

Bertil R.R. Persson, born in Oct. 12, 1938 in Malmoe, Sweden. Dr. of Philosophy and Medical Dr. Honoris causa. Full Professor in Medical Radiation Physics at the University of Lund (1980-2005). Since 1981 engaged in nuclear magnetic resonance imaging MRI, 2015 a 7-tesla imaging MRI came to Lund, which opened his interest in Schizophrenia imaging.

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Bertil R.R. Perssom

Abstract

After initial studies in the years 1960-62 in chemistry, mathematics and physics, my scientific career in medical imaging began in 1963. My qualifications in chemistry then came in handy when the Nordics' first gamma camera installed in Lund. Around the same time, the discovery of a radioactive isotope of a new element Technetium-99m showed suitable for use with the gamma camera. My task became to produce Technetium-99m radiopharmaceuticals applied for use on patients. The gamma camera images with Technetium-99m were a thousand times better than the old scintigraphy with ^{198}Au and ^{131}I. This was the beginning to my involvement in medical imaging diagnostics, which in 1981 by unfathomable ways led to my engagement in nuclear magnetic resonance imaging MRI.

In 1963, I managed together with my skilful collaborators in Lund to build the first MR scanner in Scandinavia. I nurtured a hypothesis that the soul could be mirrored with the structure of water in the brain, which the NMR relaxation of the protons could reveal. Thus, imaging nuclear spin resonance might be able to image the soul, which I thought should be there somewhere within us. However, it was mostly something about what my co-workers joked.

That became a dream until 2015 when a 7-tesla MRI device came to Lund.

Then the opportunities opened up to in vivo studies of the chemistry of the brain. This stimulated my visions of the chemistry of the soul and led to my involvement in studying brain imaging of patients with Schizophrenia that is the subject of this book:

A Story about Schizophrenia Imaging and Metabolism.
Dedicated to someone with that diagnose!

The first Chapter deals with nuclear medicine imaging of Schizophrenia that started in the early 1970s in Lund by David Ingvar and Göran Franzén. They carried out pioneering work with radioactive isotopes to image the brain's regional blood flow in Schizophrenic patients.

The introduction of SPECT with Technetium-99m radiopharmaceuticals such as e.g. ^{99m}Tc-HMPAO simplified the procedure of examining the relationships between rCBF, psychopathology and effects of neuroleptic therapy.

The introduction of positron emission tomography PET was a further improvement in nuclear medicine methods. ^{18}F-FDG PET studies of Schizophrenia show that patients with Schizophrenia have reduced brain metabolism in several brain regions.

The second chapter describes how it all began with the introduction to magnetic resonance imaging. Then follows a review of how the various magnetic resonance methods apply to Schizophrenia.

Structural brain imaging studies sMRI performed on Schizophrenic patients tend to focus on changes in anatomy and volume of different brain regions.

Altered gyrification in the Insula and Orbitofrontal Cortex appears to be a good marker for disturbances in the early neuronal development in Schizophrenia. Additional evaluation of CSF flow dynamics in the aqueduct could strengthen the knowledge about the pathophysiology in both diagnostics and treatment of patients with Schizophrenia.

Functional *f*MRI reflects changes in discrete neural circuits and may be a useful tool for defining subgroups within the clinically defined syndrome of Schizophrenia.

Diffusion tensor imaging DTI and its combination with magnetic transfer imaging MTI, show higher extracellular concentrations of free water, indicating the presence of neuro inflammation in Schizophrenia. The method of nuclear magnetic resonance (NMR) spectroscopy of the human brain developed to become a user-friendly tool for chemistry of the brain. An in vivo ^{1}H-NMR spectrum measured from the human brain at seven tesla (7 T) provide reliable quantification of more than fifteen different metabolites.

The third chapter review the main metabolic pathways in the brain of importance for Schizophrenia. ^{1}H-MRS shows that all Schizophrenia patients had a significantly lower concentration-ratio of N-AcetylAspartic acid (NAA) to Creatine in the frontal lobe than the controls.

Significantly, lower concentration-ratio of gamma-aminobutyric acid GABA to Creatine (Cr) appeared in the prefrontal cortex of patients with Schizophrenia compared to healthy controls. The results of ^{1}H-MRS also indicate that significantly lower Glutamate concentrations in the Hippocampus in Schizophrenia are associated with the pathophysiology of Schizophrenia.

Activation of the Tryptophan metabolism (TRYCAT) pathway appears to be involved in the pathophysiology of Schizophrenia. Patients with Schizophrenia seems to have significantly lower serum levels of Kynurenic-acid (KYNA), which dampens the effect of the α-7nicotinic-acetyl-choline receptor (α7nAChR) and/or the N-methyl-D-Aspartate receptor (NMDAR).

The dysfunction of those receptors seems to contribute to cognitive impairment in Schizophrenia motivating new therapeutic strategies targeting brain Kynurenic Acid synthesis.

The forth chapter review indications that other metabolite markers could promote Schizophrenia diagnosis and treatment follow-up. Out of twenty-two marker, metabolites studied, Citrate, Palmitic acid, Myoinositol and Allantoin exhibit the best ability for completely separate Schizophrenic patients from matched healthy controls, and may be useful biomarkers to monitor therapeutic efficacy.

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Keyword

Schizophrenia
Nuclear medicine
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Aqueduct
1H-MRS
Tryptophan catabolism
α7nAChR
TRYCAT

Nuclear medicine methods in Schizophrenia

The clinical use of nuclear methods started in the 1970th with studies of cerebral blood flow in Lund with David Ingvar and Franzén's use of Xenon-133 and bundles of individual detectors.

The introduction of SPECT with Technetium-99m radiopharmaceuticals such as e.g. ^{99m}Tc-HMPAO simplified the procedure and one could examine the relationships between rCBF, psychopathology and effects of neuroleptic therapy.

^{18}F-fluorodeoxyglucose (FDG)-PET shows correlations with changes in target regions of brain cognitive properties such as:

- *Amygdala* (value assignment, emotion recognition),
- Temporal-parietal connection, dorsolateral, ventromedial and Pre-frontal Cortex PFC (theory of mind and perspective),
- Medial PFC (mental activity) and
- *Striatum* (social reward).

MRI in Schizophrenia

Structural MR-imaging sMRI: Altered gyrification appears to be a significant robust marker for disturbances in early neuronal development in Schizophrenia. Increases in gyrification observed in *Bilateral Insula*, *temporal pole*, and left *Orbitofrontal Cortex*. The thickness of the frontal lobes also reflects a pathological process in Schizophrenia with reduced cortical thickness in the *Prefrontal Cortex*, *Precuneus* and *Occipital Cortex*.

CSF-MR and Schizophrenia: Evaluation of CSF flow dynamics in the aqueduct together with sMRI examinations of the brain and heart rate variability could strengthen the knowledge about the pathophysiology in both diagnostics and treatment of patients with Schizophrenia.

***f*MRI and Schizophrenia:** Dysfunction of the sensorimotor cortex (SMA) is significantly associated with motor disturbances in Schizophrenia. Language task *f*MRI data combined with structural (sMRI) can characterize Schizophrenia patients with auditory verbal hallucinations (AVH) which is one of the most common psychotic symptoms in Schizophrenia. However, no indications of clinical application of these findings appear.

Diffusion Tensor Imaging DTI studies and Schizophrenia: DTI studies of Schizophrenic patients show lower FA values than healthy controls. The FA value of the anterior part of the corpus callosum correlate negatively with the score on the scale for the assessment of negative symptoms. A negative correlation occurs between average

regional FA in the right anterior cingulum and PANSS-positive symptom scores. After cognitive training, Schizophrenia patients show significant increased FA in prefrontal-thalamic-sensory-motor connection channels.

Magnetic Transfer Imaging MTI and Schizophrenia: The great importance of magnetic transfer imaging MTI is of its combination with DTI, which show higher extracellular concentrations of free water in the brain, indicating the presence of neuro-inflammation in Schizophrenia. If the neuro-inflammation addressed early in the course of the disease, it can lead to possible recovery and perhaps prevent the progression to chronic disease.

^{1}H-MRS and Schizophrenia

N-acetyl aspartate NAA: A meta-analysis shows that N-acetyl aspartate NAA-concentrations are lower in the frontal lobe and Thalamus in patients with first episode psychosis compared to controls.

Glutamate: A systematic review of all ^{1}H-MRS studies up to the year 2022 of Glutamate changes in patients with early phase psychosis showed no definite evidence of Glutamate changes in areas of the *Hippocampus*, *Cerebellum*, *Thalamus* and medial prefrontal region.

Gamma-Amino-Butyric-Acid GABA: Schizophrenia patients show significantly lower GABA to Creatine Cr ratios in the prefrontal cortex compared to healthy controls

Glutamine: Schizophrenia patients show significantly, elevated levels of Glutamine as well as elevated ratio of Glutamine to Glutamate, while the level of Glutamate is unchanged compared to healthy controls.

Choline: The results of ^{1}H-MRS studies suggest that choline increases in both the prefrontal and occipital cortex during recent onset Schizophrenia indicating signs of neuro inflammation.

Tryptophan catabolism and Schizophrenia

Tryptophan: Tryptophan is one of the essential amino acids, which the body cannot produce by itself, and which therefore supplies through food intake.

The Serotonin pathway: In the Serotonin pathway, Tryptophan (TPH) convert Serotonin (5HT) which further metabolize to form Melatonin

The Kynurenine pathway: In the Kynurenine pathway, 90% of Tryptophan breakdown takes place through conversion to Kynurenine via the enzyme *Tryptophan2,3-dioxygenase* (TDO) in the liver. The remaining 10% of the breakdown to Kynurenine takes place by the enzyme *Indolamine 2,3-dioxygenase* (IDO) in the brain, GI tract and liver. Kynurenine metabolize to Quinolinic acid QA, which convert to *Nicotinamide-Adenine-Dinucleotide* (NAD) that is a coenzyme central to metabolism. NAD exists in two forms: an oxidized form abbreviated as NAD+ and a reduced form NADH (H for hydrogen).

Tryptophan Metabolism pathway and Schizophrenia: Activation of the Tryptophan Metabolism (TRYCAT) pathway appears to be involved in the pathophysiology of Schizophrenia. Patients with Schizophrenia compared to healthy controls show significant differences for Tryptophan metabolites in the CNS, which may ultimately affect glutamate neurotransmission via N-methyle-D-aspartate and α-7Nicotin receptors.

α7nAChR as a therapeutic target in Schizophrenia: A number of Tryptophan metabolites known to be neuroactive and potential associated with cognitive deficits in Schizophrenia. Among these metabolites are Kynurenic acid (KYNA), 5-HydroxyIndole (5-HI) and Quinolinic acid (QUIN). These metabolites act with different effects on the α-7nicotine-acetyl-choline receptor (α7nAChR) and/or the N-Methyl-D-aspartate receptor (NMDAR).

Kynurenic acid (KYNA) is thought to contribute to cognitive impairment in Schizophrenia, while Quinolinic acid QA which is an

α7nicotinic agonist appears to have positive effects on neurocognition in people with Schizophrenia.

Nicotine, which is a low-potency agonist for the α7nAChR receptor, has some beneficial effects on neurophysiological and neurocognitive deficits associated with Schizophrenia, suggesting that more efficient receptor activation may meaningfully improve cognition in Schizophrenia.

Tryptophan metabolism (TRYCAT) and Schizophrenia: CSF levels of Kynurenic acid are elevated in Schizophrenia, motivating new therapeutic strategies targeting brain Kynurenic acid synthesis. Studies in animal models indicate that high levels of Tryptophan suppress aggressive behavior, probably related increased central Serotonin availability.

Abstrakt

Nukleärmedicinska metoder vid schizofreni

Den kliniska användningen av nukleära metoder startade på 1970-talet med studier av hjärnblodflödet i Lund med David Ingvars och Franzéns användning av Xenon-133 och buntar av enskilda detektorer.

Införandet av SPECT med Teknetium-99m radiofarmaka som t.ex. 99mTc-HMPAO förenklade proceduren och man kunde undersöka sambanden mellan rCBF, psykopatologi och effekter av neuroleptisk terapi.

18F-fluorodeoxiglukos (FDG)-PET visar korrelationer med förändringar i målregioner av hjärnans kognitiva egenskaper som:

- Amygdala (värdetilldelning, känsla igenkänning),
- Temporal-parietal koppling, dorsolateral, ventromedial och Prefrontal Cortex PFC (teori om sinne och perspektiv),
- Medial PFC (mental aktivitet) och
- Striatum (social belöning).

MR vid schizofreni

Strukturell MR-avbildning sMRI: Förändrad gyrifiering verkar vara en betydande robust markör för störningar i tidig neuronal utveckling vid schizofreni. Ökning av gyrifiering observerad i Bilateral Insula, temporal pol och vänster Orbitofrontal Cortex. Tjockleken på frontalloberna speglar också en patologisk process vid schizofreni med minskad kortikal tjocklek i Prefrontal Cortex, Precuneus och Occipital Cortex.

CSF-MR och Schizofreni: Utvärdering av CSF-flödesdynamik i akvedukten tillsammans med sMRI-undersökningar av hjärnan och hjärtfrekvensvariabilitet skulle kunna stärka kunskapen om patofysiologin i både diagnostik och behandling av patienter med schizofreni.

fMRI och schizofreni: Dysfunktion av den sensorimotoriska cortex (SMA) är signifikant associerad med motoriska störningar vid schizofreni. Språkuppgift •MRT-data kombinerat med strukturell (sMRI) kan karakterisera schizofrenipatienter med auditiva verbala hallucinationer (AVH) som är ett av de vanligaste psykotiska symtomen vid schizofreni. Det finns dock inga indikationer på klinisk tillämpning av dessa fynd.

Diffusion Tensor Imaging DTI-studier och schizofreni: DTI-studier av schizofrena patienter visar lägre FA-värden än friska kontroller. FA-värdet för den främre delen av corpus callosum korrelerar negativt med poängen på skalan för bedömning av negativa symtom. En negativ korrelation uppstår mellan genomsnittlig regional FA i höger anterior cingulum och PANSS-positiva symptompoäng. Efter kognitiv träning visar schizofrenipatienter signifikant ökad FA i prefrontala-talamus-sensorisk-motoriska anslutningskanaler.

Magnetic Transfer Imaging MTI och schizofreni: Den stora betydelsen av magnetisk transfer imaging MTI är dess kombination med DTI, som visar högre extracellulära koncentrationer av fritt vatten i hjärnan, vilket indikerar närvaron av neuroinflammation vid

schizofreni. Om neuroinflammationen åtgärdas tidigt i sjukdomsförloppet kan det leda till eventuell återhämtning och kanske förhindra utvecklingen till kronisk sjukdom.

1H-MRS och schizofreni

N-acetylaspartat NAA: En metaanalys visar att N-acetylaspartat NAA-koncentrationerna är lägre i frontalloben och Thalamus hos patienter med första episod psykos jämfört med kontroller.

Glutamat: En systematisk genomgång av alla 1H-MRS-studier fram till år 2022 av glutamatförändringar hos patienter med psykos i tidig fas visade inga säkra bevis på glutamatförändringar i områden av Hippocampus, lillhjärnan, thalamus och mediala prefrontala regionen.

Gamma-amino-smörsyra-GABA: Schizofrenipatienter visar signifikant lägre GABA till kreatin Cr-kvoter i den prefrontala cortex jämfört med friska kontroller

Glutamin: Schizofrenipatienter visar signifikant förhöjda nivåer av glutamin såväl som förhöjda förhållande mellan glutamin och glutamat, medan nivån av glutamat är oförändrad jämfört med friska kontroller.

Kolin: Resultaten av 1H-MRS-studier tyder på att kolin ökar i både den prefrontala och occipitala cortex under nyligen debuterad schizofreni, vilket indikerar tecken på neuroinflammation.

Tryptofankatabolism och schizofreni

Tryptofan: Tryptofan är en av de essentiella aminosyrorna, som kroppen inte kan producera själv, och som därför tillförs genom födointag.

Serotoninvägen: I serotoninvägen omvandlar tryptofan (TPH) till serotonin (5HT) som vidare metaboliseras till melatonin

Kynureninvägen: I Kynureninvägen sker 90 % av tryptofannedbrytningen genom omvandling till Kynurenin via enzymet Tryptofan2,3-dioxygenas (TDO) i levern. De återstående 10 % av nedbrytningen till Kynurenin sker av enzymet Indolamin 2,3-dioxygenas (IDO) i hjärnan, mag-tarmkanalen och levern. Kynurenin metaboliseras till kinolinsyra QA, som omvandlas till nikotinamid-adenin-dinukleotid (NAD) som är ett koenzym som är centralt för metabolismen. NAD finns i två former: en oxiderad form förkortad som NAD+ och en reducerad form NADH (H för väte).

Tryptofanmetabolismväg och schizofreni: Aktivering av tryptofanmetabolismvägen (TRYCAT) verkar vara inblandad i patofysiologin för schizofreni. Patienter med schizofreni jämfört med friska kontroller visar signifikanta skillnader för tryptofanmetaboliter i CNS, vilket i slutändan kan påverka glutamat-neurotransmission via N-metyl-D-aspartat- och α-7-nikotinreceptorer.

α7nAChR som ett terapeutiskt mål vid schizofreni: Ett antal tryptofanmetaboliter som är kända för att vara neuroaktiva och potentiella associerade med kognitiva underskott vid

schizofreni. Bland dessa metaboliter finns Kynurensyra (KYNA), 5-HydroxyIndol (5-HI) och Kinolinsyra (QUIN). Dessa metaboliter verkar med olika effekter på α-7nikotin-acetyl-kolinreceptorn (α7nAChR) och/eller N-Methyl-D-aspartatreceptorn (NMDAR).

Kynurensyra (KYNA) tros bidra till kognitiv försämring vid schizofreni, medan **kinolinsyra QA** som är en α7nikotinsyraagonist verkar ha positiva effekter på neurokognition hos personer med schizofreni.

Nikotin, som är en lågpotens agonist för α7nAChR-receptorn, har vissa fördelaktiga effekter på neurofysiologiska och neurokognitiva brister associerade med schizofreni, vilket tyder på att effektivare receptoraktivering på ett meningsfullt sätt kan förbättra kognitionen vid schizofreni.

Tryptofanmetabolism (TRYCAT) och schizofreni: CSF-nivåer av Kynurensyra är förhöjda vid schizofreni, vilket motiverar nya terapeutiska strategier inriktade på hjärnans Kynurensyrasyntes. Studier i djurmodeller indikerar att höga nivåer av tryptofan undertrycker aggressivt beteende, troligen relaterat till ökad central serotonintillgänglighet.