

# Nuclear medicine in psychiatry

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## Introduction

From the second half of the twentieth century, advances in biological and psychopharmacological research seemed to promise a swift discovery of an organic basis of psychiatric diseases. Today we know that biological research in psychiatry is not a success story. This may be due to the complicated character of psychiatric disorders, where it is difficult to establish a unified model of the disease and thus in many cases difficult to fit into any categorical classification. This also affects the role of nuclear medicine (NM) in psychiatry.

## Diagnosis in psychiatry

Today's diagnosis in psychiatry largely relies on the classification of diseases following the criteria of the Diagnostic and Statistical Manual of Mental Diseases (DSM-IV-TR-2000) [1]. This classification enabled better definition of nosological concepts and better communication and understanding between psychiatrists.

On the other hand, DSM-IV does not entirely fit the psychiatric diagnosis due to its rigid application of choice principle (five out of nine symptoms).

There are two major problems in psychiatric diagnosis as a whole:

- **diversity of symptoms** — depressive episode patients may be either agitated and insomniac, or with psychomotor retardation and hypersomnia.
- **overlapping symptoms** — (sometimes defined as “co-morbidity”); e.g. 30–60% of depressive patients may have co-morbid anxiety disorder, whereas 40% diagnosed with anxiety have [2].

## Diagnosis in psychiatry — the role of neuroimaging

In the same way that the symptoms between different diseases in psychiatry overlap, functional brain research frequently shows

the same pattern of changes across diagnostic borders; on the other hand, many the other tests, e.g. psychological tests, present the same problem as mentioned above; therefore:

The psychiatrist seldom applies to an NM specialist to obtain a diagnosis; instead, a nuclear medicine report will rather confirm, or less frequently exclude, the psychiatrist's diagnosis. Ideally, psychiatric patients should be rescanned after the treatment, and changes in perfusion and/or metabolism discussed between psychiatrist and NM specialist.

## Applications of nuclear medicine

Applications of NM can be divided into:

- I. Mostly diagnostic/practical/clinical:
  - differential diagnosis of dementia;
  - psychiatric sequelae of head trauma, including late whiplash syndrome;
  - neuropsychiatric lupus erythematosus.
- II. With mixed/indeterminate status:
  - psychiatric disorders in parkinsonian syndromes;
  - chronic fatigue/myalgic encephalomyelitis.
- III. Mostly investigational/experimental:
  - other/most receptor studies.

## Differential diagnosis of dementia

There are five potential major roles for neuroimaging with respect to dementia:

- as a cognitive neuroscience research tool;
- for the prediction of which normal or slightly impaired individuals will develop dementia and over what time frame;
- for early diagnosis of Alzheimer's disease (AD) in demented individuals, (sensitivity) and separation of AD from other forms of dementia (specificity);
- for monitoring disease progression;
- for monitoring response to therapy.

## Alzheimer's disease — SPECT studies

Single photon emission-computed tomography (SPECT) of regional cerebral blood flow (rCBF) reaches detecting AD in up to 81%; although the clinical criteria may more sensitive (up to 81%), SPECT seems superior in differentiating AD from the other types of dementia (91% vs. 70%) [3]. Applying novel methodological approaches such as means clustering or principal component analysis has improved SPECT accuracies to as much as 98 and 90%, respectively [4].

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In SPECT studies, the typical finding is decreased blood flow in the parietal or temporal lobe; in advanced cases with poor prognosis, decreased blood flow in the frontal lobes is also found. In mild cognitive impairment, rCBF SPECT studies may differentiate patients who will convert to AD from non-converters. Converters show reduced rCBF in bilateral temporo-parietal areas and the precuneus, compared with non-converters. The logistic regression model reveals that reduced rCBF in the inferior parietal lobule, angular gyrus and precuneus has a high predictive value and discriminative ability [5]. The acetazolamide test in rCBF SPECT is helpful to differentiate AD from vascular dementia [6].

Following the therapy with acetyl cholinesterase inhibitors (AChEi), the regional cerebral blood flow increases or remains stable in AD patients with stabilized cognitive performance during therapy, but decreases in non-responders [7].

### Alzheimer's disease — metabolic studies

[(18)F] fluorodeoxyglucose (FDG) positron emission tomography (PET) images of AD demonstrate a focally decreased cerebral metabolism especially involving the posterior cingulate and neocortical association cortices, while largely sparing the basal ganglia, thalamus, cerebellum and cortex mediating primary sensory and motor functions.

In a multicentre study comprising 10 PET centres (Network for Efficiency and Standardisation of Dementia Diagnosis, NEST-DD) that employed an automated voxel-based analysis of FDG-PET images, the distinction between controls and AD patients was 93% sensitive and 93% specific, and even in very mild dementia (at MMSE 24 or higher) sensitivity was still 84% at 93% specificity [8]. In very mild AD, both FDG-PET and voxel-based morphometry (VBM-MRI) had high accuracies for diagnosis, but FDG-PET showed a slightly higher accuracy than VBM-MRI. A combination of the two techniques will yield a higher diagnostic accuracy in very mild AD by making full use of functional and morphological images [9].

In addition to glucose metabolism, specific tracers for dopamine synthesis (<sup>18</sup>F-F-DOPA) and for (<sup>11</sup>C-MP4A) are of interest for differentiation among dementia subtypes. Cortical acetylcholine esterase activity (AChE) is significantly lower in patients with AD or dementia with Lewy bodies (DLB) than in age-matched normal controls. In DLB there is also an impairment of dopamine synthesis, similar to Parkinson's disease.

### Alzheimer's disease — imaging amyloid deposits

Pathologically, AD is characterised by the excess accumulation of two types of protein aggregates: amyloid  $\beta$ -peptide ( $A\beta$ ) plaques and neurofibrillary tangles.

Amyloid imaging with SPECT is possible with radioiodinated styrylpyridines and hydroxybenzothiazoles [10], but today, practically, PET is the only available  $A\beta$  imaging technique with the following agents:

- fluorophore derivative <sup>18</sup>F-FDDNP [11];
- benzothiazole derivative <sup>11</sup>C-PIB [12];
- stilbene derivative <sup>11</sup>C SB-13 [13];

— <sup>18</sup>F-fluoropegylated diphenylacetylenes [14].

Due to high costs, these modalities remain solely investigational.

### Differential diagnosis of dementia — DLBD

Diffuse Lewy body dementia (DLBD) is the second most common type of degenerative dementia after AD and accounts for 15–20% of all autopsy-confirmed dementias in old age. Core clinical features are progressive cognitive impairment, visual hallucinations and parkinsonian symptoms and signs. In DLBD there is a pronounced cholinergic deficit, therefore, cholinergic medication gives better results, than in AD. In its early stages, DLBD brings difficulties in differentiation with AD.

On rCBF SPECT scanning, patients show hypoperfusion in parietal and occipital, and in frontal lobes, called “horseshoe” signs [15]. Combined studies of MMSE and brain SPECT achieved a high discrimination between DLB and AD with a sensitivity of 81% and a specificity of 85%, suggesting that this is a useful and practical approach to differentiate DLB from AD [16]. (18)F-FDG PET showed significant glucose metabolic reductions in the temporal, parietal and frontal areas (including the occipital lobe) compared with those in the control group; in contrast, in AD patients, both the hippocampal volume and glucose metabolism were significantly decreased, whereas the occipital volume and metabolism were preserved [17].

### Fronto-temporal dementia

Fronto-temporal dementia (FTD) generally has a presenile onset, behavioural problems dominate the clinical picture and cognitive functions are still relatively intact.

In rCBF SPECT studies, rCBF defect in frontal lobes in the left temporoparietal-occipital discriminates FTD and AD and with a sensitivity of 0.8 and specificity 0.65. [18, 19].

In PET studies in early stages of FTD, the neurodegenerative process was found to be limited to the frontal lobes. During the progression of the disease, the pathological changes pass over the lobar borders and spread into the parietal and temporal cortices [20]. In the late stages a significant hypometabolism is found mostly in extensive prefrontal areas, cingulate gyri, anterior temporal regions and the left inferior parietal lobule. Frontal hypometabolism is usually more prominent in the left hemisphere than in the right — in 79% of patients [21].

Therefore sociopathy in FTD may result from right fronto-temporal dysfunction. In many jurisdictions, FTD patients with sociopathy would not pass legal criteria for “not guilty” due to insanity.

### Dementia in Parkinson's disease / Parkinsonian syndromes

Parkinson's disease is a neurodegenerative disorder characterised by progressive damage of the nigrostriatal dopaminergic neurons in the basal ganglia. It accounts for up to 85% of patients with parkinsonian symptoms.

Parkinsonian syndromes is a broader definition that encompasses other movement disorders with symptoms resembling PD

and includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal degeneration.

Confusingly, the symptoms of PD or PS can also be met in patients with essential tremor or secondary to some medications. Therefore, up to 25% of patients initially diagnosed as PD, later have this diagnosis changed. 20–30% of patients with PD have dementia; the crucial problem of diagnosing it with, for example, MMSE are motor and speech disturbances.

PD patients with dementia show left temporo-parietal hypoperfusion as compared to a group of patients without dementia, which resembles perfusion deficits described in Alzheimer's disease. Hypoperfusion of the left temporal lobe with an increase of rCBF within the left thalamus might be clinically useful in the discrimination of Parkinson's disease patients with dementia from those without cognitive impairment [22].

Another aspect of RN diagnosis aims to differentiate PD and essential tremor by  $^{123}\text{I}$ - $\beta$ -CIT or  $^{18}\text{F}$ -DOPA uptake and differentiating PD and PS-plus syndromes with imaging of  $\text{D}_2$  receptors with  $^{123}\text{I}$ -IBZM [23–25].

### Post-traumatic disorders

After head trauma a number of neuropsychiatric symptoms and signs may follow, with considerable difficulties both in the treatment and in medical certification of posttraumatic neuropsychiatric disorders for the purpose of criminal and civil law proceedings.

Functional brain imaging data collected in a resting state can provide objective evidence of brain injury in mild blunt head trauma patients with persistent postconcussive somatic and/or cognitive symptoms, particularly in mild and moderate traumatic brain injury by better sensitivity than MR/CT findings and providing an important exclusion role [26, 27], e.g. young patients following head trauma 97% with negative rCBF SPECT findings develop no post-traumatic disorder, whereas 95% with rCBF changes do. RCBF SPECT scanning is particularly useful in imaging blood flow disturbances in basal ganglia following head traumas, as well as in mild brain injury [26–27]. The results of rCBF scanning are important in rehabilitation counselling, medico-legal arguing and the evaluation of the ability of the patient to work. Its limitations overlap diffuse axonal injury (DAI), invisible in PET/SPECT, and in older patients overlapping, for example, atherosclerotic vascular lesions.

### Late whiplash syndrome

The prevalence of whiplash injury is 4 cases per 1000 inhabitants per year, usually following rear-end car collisions. This sometimes results in whiplash-associated disorder (WAD), a controversial condition with largely unknown pathogenetic mechanisms. Only a small proportion (up to 5%) of whiplash injury patients develop late whiplash syndrome with cerebral symptoms: headache, dizziness, vertigo and concentration, attention and memory disturbances, as well as peripheral symptoms: neck pain, neck rigidity, temporomandibular dysfunction.

Being frequently secondary to traffic, sport and work related accidents, late whiplash syndrome is a major medico-legal prob-

lem, of interest not only to physicians, but also to lawyers and insurance companies.

### Late whiplash syndrome — triggering Alzheimer's disease?

In 1997–2003 Otte et al. described an increased parieto/occipital hypoperfusion and hypothesized that LWS may trigger Alzheimer's disease following prolonged hypoperfusion in the cortico-basal region [28–30].

This hypothesis has been heavily criticized by many opponents, eg. Sundström and colleagues, who showed rCBF changes in patients with chronic back pain of non-traumatic origin, but not in those following whiplash injury [31], whereas some data supports it [32].

### Neuropsychiatric involvement in systemic lupus erythematosus

The peak incidence of systemic lupus erythematosus (SLE) occurs between 15 and 40 years of age. Central nervous system (CNS) manifestations have been described in 20–70% of cases. This dispersion alone illustrates the basic problem of cerebral involvement in SLE, i.e. differentiating organic brain lesion from functional disturbances, influence of medication — particularly steroids, feelings of social rejection following skin changes, etc. Neuropsychiatric manifestations in SLE comprise: migraine, epilepsy and stroke, cognitive dysfunction, mood disorder, anxiety disorder, acute confusion state and psychoses.

Radionuclide studies help to distinguish organic brain lesions and to differentiate from functional/iatrogenic changes. The clinician expects a zero/one answer to the question: is there CNS involvement or not?

As a “golden standard” of neuroimaging in neuropsychiatric systemic lupus erythematosus (NP-SLE) is considered, MRI scanning with white matter hyperintensities (WMH) as a marker of vascular involvement. However, this appears in 30% of SLE patients without CNS involvement and is absent in the early/intermediate stages of the disease.

As a result, rCBF SPECT scanning is the most sensitive, although not entirely specific for neuroradiological assessment in NP SLE and other loose connective tissue diseases [33]. The higher sensitivity of SPECT, compared with MRI, can be explained by the vasculopathy with microcirculation changes as a major pathological factor in SLE.

$^{18}\text{F}$ FDG PET scanning shows “posterior” type hypometabolism as a typical finding [34].

### Schizophrenia

Schizophrenia is a major source of morbidity worldwide, with a prevalence of about 1% and significant disablement. RN neuroimaging is focused on receptor research, with few results, mostly indicating disturbances of dopamine in schizophrenia, but this is unlikely to be the whole story. As new ligands are developed, further insights will be gained into the underlying pathology of schizophrenia; new techniques combining functional imaging with genetic studies are likely to not only depict the state of receptor populations, but also concentrate on long-term dynamic changes induced by the illness and its treatment.

### **Schizophrenia — the dopamine overactivity hypothesis**

This hypothesis says that increased activity in the dopamine neurotransmitter system is responsible for the positive symptoms of schizophrenia. An increased density of D<sub>2</sub> receptors was found in post-mortem studies [35].

Early studies revealed a marked increase in D<sub>2</sub> binding within the striatum. Further studies revealed two distinct families of dopamine receptors: D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) and D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>). It could be that the antipsychotic drug selectivity could be due to preferential binding of dopamine D<sub>2</sub>-like receptors.

For measuring dopamine synthesis and transport in presynaptic function for the former, the most commonly used tracers are 6-[(18)F]FDOPA and 6-[(18)F]FMT, whereas for the latter, several (11)C/(18)F-labelled tropane analogues are being clinically used. Postsynaptically, dopamine exerts actions through several subtypes of the dopamine receptor [36].

In schizophrenia, dopamine studies of receptor competition of <sup>123</sup>I-IBZM, a dopamine D<sub>2</sub> ligand with dopamine, showed that not only resting dopamine levels matter, but also suggested that schizophrenia is a disorder of dopamine dysregulation in different parts of the brain. In treatment follow-up, increasing D<sub>2</sub> receptor occupancy on the 2<sup>nd</sup> SPECT was a predictive factor for the relapse; therefore, D<sub>2</sub> receptor occupancy and its changes during quetiapine therapy is thought to be related to the prognosis of the treatment efficacy [37].

### **Schizophrenia — 5HT receptors**

An interest in the role of 5HT<sub>2a</sub> receptors in schizophrenia was aroused by the observation that serotonergic agents, such as LSD, led to hallucinations. Initial SPECT and PET studies showed a very high occupancy of 5HT<sub>2a</sub> receptors for many atypical antipsychotic drugs including clozapine, olanzapine and risperidone but not typical ones like haloperidol and chlorpromazine. The involvement of 5HT<sub>2a</sub> receptors was undermined by the fact that its pure antagonists did not have any antipsychotic effect. More recent papers on 5HT<sub>1a</sub> have shown increased binding in schizophrenics in the left mediotemporal cortex, but the meaning of this is unclear [38]. The current view is that changes in this receptor population are unlikely to be a causal factor in schizophrenia.

### **Schizophrenia — glutamate and NMDA receptors**

N-Methyl-D-aspartate (NMDA) receptors are calcium-permeable glutamate receptors that play putative roles in learning, memory and excitotoxicity. There has been much interest over the years in the NMDA receptors in schizophrenia, as certain blockers of NMDAR such as PCP and ketamine lead to transient drug-induced symptoms very similar to those reported by schizophrenic patients. The first *in vivo* evidence of an NMDA receptor deficit in medication-free schizophrenic patients was published in 2006 [39].

### **Mood disorders**

Mood disorders are amongst the most prevalent in modern society and have an important socio-economic impact.

Diagnosing depression is based upon fulfilling five criteria of the American Psychiatric Association/DSM-IV, including at least "depressed mood" or "diminished interest of pleasure"

during the same 2-week period. The presence of manic or hypomanic episodes further specifies whether the disorder is unipolar or bipolar.

The course specifiers describe the severity of the last episode, from mild to severe, and the course of disorders, e.g. recurrent, with seasonal pattern or with rapid cycling pattern; other specifiers describe atypicality, postpartum onset and the presence of catatonic features or chronicity.

### **Brain perfusion and metabolism studies in depressive disorders**

Early studies by Baxter et al. described a globally decreased supratentorial brain activity in bipolar disorders. With metabolic rate increasing while going from depression to euthymic or manic state, further studies showed a significant left-right prefrontal asymmetry, resolving after treatment. Hypoperfusion in recurrent depressive disorders was considerably greater (nearly significant) in comparison with the first depressive episodes [40].

Further studies refined the findings of prefrontal hypoperfusion/metabolic hypoactivity, as the most important delineating those findings to areas of the prefrontal cortex and its functionally separate areas: dorsolateral (DLPFC), the orbito-frontal and anterior cingulate, left amygdala, parahippocampal gyrus [41, 42], which with subcortical circuits have separate behavioural functions: DLPFC mediating executive functions, orbito-frontal object-affect associations and anterior cingulate mediating motivation.

### **Mood disorders — treatment effects**

Nearly all available antidepressants have been studied. Normalisation of the frontal hypoperfusion/hypometabolism and/or asymmetry appears to be the most replicative finding [43, 44].

In many studies a pattern of cortical flow/metabolism increases and limbic/paralimbic decreases was seen in association with chronic treatment, which suggest primary subcortical and limbic effects of pharmacological treatment, with neocortical effects as secondary [45].

Electroconvulsive therapy (ECT), a powerful tool where pharmacological intervention fails, initially reduces the CBF and metabolism in the short term, suggesting the reduction of neural activity; in the long-term, normalising perfusion/metabolism in depressed patients [43, 46]. However, ECT flow/metabolism results may be atypical, as this therapy is mostly applied in treatment-resistant patients.

Repetitive transcranial magnetic stimulation (rTMS) of the prefrontal cortex may be useful in refractory cases. High-frequency rTMS of the left prefrontal cortex and possibly of the opposite physiological effects low frequency rTMS of the right prefrontal cortex produce a significant decrease in Hamilton depression scale scores; it increases the metabolic rate in the prefrontal cortex, amygdala, basal ganglia, hippocampus and cerebellum; post-treatment a decrease in cingulate [47].

Vagal nerve intermittent electrical stimulation, used mostly in epilepsy treatment, also reduces depressive symptoms. rCBF changes share features with changes of rCBF previously associated with the administration of selective serotonin reuptake inhibitors. Similarities to other brain-stimulation strategies in antidepressant treatment were less pronounced [48].

### **Radioligand receptor studies in depression**

These studies are limited mainly by the availability of suitable ligands. Currently available ligands allow the investigation of 5-HT<sub>1A</sub> [11C-WAY-100635], 5-HT<sub>2A</sub> [<sup>123</sup>I]-ketanserin, <sup>18</sup>F-altanserin, and <sup>11</sup>C-methylpiperone] and D<sub>2</sub> receptors [<sup>123</sup>I-IBZM]. The results are rather discordant [49, 50].

Most, albeit not all, studies find an increased 5-HT<sub>2A</sub> binding after treatment, the same effect in D<sub>2</sub> binding and a decrease in HT<sub>1A</sub> binding.

The current status of ligand studies in depression does not yet allow for the tailoring of the pharmacotherapeutic status in individual patients. They allow at least some agreement as to the effect of antidepressant agents on the HT and dopamine receptors and on serotonin transporters.

There are two conclusions about radionuclide studies in depression: good news: brain imaging is a powerful tool to explore various aspects of brain function in depression; bad news: the clinical psychiatrist should not ask the nuclear medicine psychiatrist to confirm the diagnosis of depression in his patients — hypofrontality is quite an unspecific finding. Performing functional imaging, however, should stimulate both specialists to look at functional abnormalities on the scan and to link them to the patients' behavioural abnormalities and/or symptoms.

Future research should be devoted to finding the basics of treatment regimens and finding predictors of treatment response.

### **Obsessive-compulsive disorder**

Obsessive-compulsive disorder (OCD) is characterised by repetitive thoughts, impulses, images or behaviours. The obsessions or compulsions interfere significantly with the person's normal life as well as occupational and social functioning.

Neuroimaging studies have proved that the evidence of the dysfunction of the fronto-subcortical circuit might be involved in the pathophysiology of OCD. In SPECT and PET studies hyperactivities of those circuits, including orbito-frontal cortex, anterior cingulate and/or basal ganglia, have been a consistent finding [51].

Serotonin transporter studies indicate a reduced serotonergic input into the fronto-subcortical circuits in OCD, thereby diminishing the inhibitory regulation of serotonin in these circuits [52].

Fluvoxamine treatment significantly improves clinical symptoms and increases D<sub>2</sub> ligand [(11C)-raclopride binding potential (BP) in the basal ganglia of OCD patients. (Chronic treatment with fluvoxamine induces a slight but significant increase in striatal [(11C)-raclopride binding of previously drug-naive OCD patients [53].

Although present imaging techniques have limitations as a means of brain dysfunction in OCD, nuclear neuroimaging may be used as an objective tool and as a way to predict a response to the treatment.

### **Eating disorders**

Eating is part of basic human behaviour. Therefore, eating disorders are relative rare within the domain of psychiatry. There are two major pathological entities: anorexia nervosa and bulimia nervosa. On the other hand, a separate major issue is the investigation of the CNS in binge-eating and obesity: a major epidemic

problem. Many obese patients probably suffer from binge-eating disorders, but this is certainly not always objectified and is even overlooked.

Functional brain imaging in eating disorders has been available for more than a decade. Generally there is an enormous differentiation between studies, and they may be secondary to methodological variations. Therefore they are of limited, or even no clinical value, at least at present, although they may give some guidance to future pharmacological studies.

### **Anorexia nervosa**

Anorexia nervosa (AN) is a devastating and life-threatening disease. Among females, its prevalence is approximately 0.27–1% [54]. There are two subtypes: in the RAN subtype, dieting, fasting or excessive exercise is used to achieved weight loss; the binge-eating/purging type involves a combination of binge eating and purging by means of self-induced vomiting and/or misuse of laxatives, diuretics and enemas.

Patients with anorexia nervosa show either hyperperfusion in the frontal, fronto-temporal and parietal cortex or hypoperfusion in the anterior cingulate. Activation tests show an rCBF increase in the left inferior frontal lobes. Following treatment, changes of rCBF in the right DLPFC, ACC, MPFC, PCC and precuneus are related to the AN recovery process and might be associated with the improvement of interoceptive awareness [55].

Receptor [<sup>18</sup>F-altanserin] HT<sub>2A</sub> studies showed reduced tracer binding with altered neurotransmission during recovery. The question remains, whether it is a cause or consequence of AN.

There are two basic technical problems in the assessment of AN patients: rCBF changes are either small and space-restricted or diffuse and unspecific. This requires either good quality statistical parametric mapping (SPM) or activation paradigms utilising food stimuli in a well-standardized environment.

### **Bulimia nervosa**

Bulimia (Greek — *bull hunger*) is generally considered a condition in which the subject engages in recurrent binge eating followed by an intentional purging. This purging is done in order to compensate for the excessive intake of food and to prevent weight gain. Purging typically takes the form of vomiting; inappropriate use of laxatives, enemas and other medication and/or excessive physical exercise. Historically, it was initially considered a variant of anorexia nervosa.

SPECT studies showed decreased right inferior frontal and left temporal lobes. This may suggest hypoactivity of the putative feeding suppression mechanism in the frontal lobe, resulting in hyperphagia. Alterations in rCBF during the ill state of BN may be a state-related phenomenon that remits with recovery [56].

PET study data showed — contrary to depressive patients — maintained basal ganglia metabolism. Some PET studies showed lower rCMRGlucose patterns similar to those of obsessive-compulsive disorder symptoms.

Receptor studies suggest decreased serotonergic transmission in bulimia nervosa. Studies using PET with serotonin specific radioligands implicate alterations of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors and the 5-HT transporter. Alterations of these circuits may affect mood and impulse control as well as the motivating and hedonic aspects of feeding behaviour [57].

## Obesity

Obesity is an epidemic of our age, at least in some countries; therefore, functional brain studies in obesity seem very promising. rCBF SPECT studies in obese women showed higher CBF in the right parietal and temporal cortices during food exposure than in control conditions. In addition, in obese women the activation of the right parietal cortex was associated with an enhanced feeling of hunger when looking at food. No such changes or associations were seen in normal-weight women [58].

In PET studies, higher metabolic activity was shown in the area of the parietal cortex where the somatosensory maps of the mouth, lips and tongue are located, suggesting the role of a reward component in the aetiology of obesity. Another study showed the involvement of enhanced sensitivity of the frontal regions following food stimuli, suggesting their specific response.

Receptor studies with  $^{11}\text{C}$ -raclopride showed the negative correlation of BMI and  $\text{D}_2$  receptor availability [59].

## Social anxiety disorder

Social anxiety disorder (SAD) is characterised by the fear of social interaction and performance situations. A person fears that he or she will act in a way that will be humiliating or embarrassing [DSM-IV]. In the course of the disease, secondary depression or subsequent alcohol abuse and dependence may develop.

rCBF SPECT scanning data are similar to those of other anxiety disorders and are consistent with previous work demonstrating the importance of limbic circuits in this spectrum of disorders. These play a crucial role in cognitive-affective processing, are innervated by serotonergic neurons, and changes in their activity during serotonergic pharmacotherapy seem crucial [60].

Serotonin receptor studies showed that the lower  $5\text{-HT}_{1\text{A}}$  binding in the amygdala and mesiofrontal areas of SAD patients was consistent with a previous PET study in healthy volunteers showing an inverse correlation between  $5\text{-HT}_{1\text{A}}$  BP and state anxiety and other human PET studies in patients with panic disorders showing reduced  $5\text{-HT}_{1\text{A}}$  binding, thus corroborating the potential validity of  $5\text{-HT}_{1\text{A}}$  receptors as targets in the treatment of human anxiety disorders [61].

Dopamine receptor studies showed that striatal dopamine reuptake site densities were markedly lower in patients with social phobias than in the age- and gender-matched comparison subjects. These results indicate that social phobia may be associated with a dysfunction of the striatal dopaminergic system [62].

## Functional brain imaging in court

PET and SPECT studies are increasingly used as tools in forensic medicine, particularly in the USA since the start of the nineties. The mental disorders which attract the most legal attention are those where a connection is made to an injurious stimuli, e.g. post-traumatic brain injury or post-traumatic stress disorder. The brain changes are not clear in all patients; therefore, functional neuroimaging cannot be safely used to make diagnosis of psychiatric disorders or to exclude/confirm psychiatric disorders, so its use is limited to that of an auxiliary tool together with CT, MRI and psychometric testing, although some specific reports exist [63, 64].

In order to be accepted as evidence, the Supreme Court of the USA ruled that the following elements should be taken into account assessing the diagnostic method [65]:

- can the particular method be tested?
- are the known/potential pitfalls of the method established?
- is there sufficient scientific evidence about the method?
- is there wide acceptance of the method in the scientific world?

In most cases, PET and SPECT fulfil the above-mentioned demands, at least partly, due to the scarce number of controlled studies, low sensitivity and specificity, and insufficient standardisation. They have, therefore, been used in only a few situations: traumatic brain injury following car accidents or criminal attacks, in confirming/excluding brain injury in victims with unspecific complaints such as persistent headaches, amnesia, emotional disorders etc., organic basic brain dysfunction e.g. frontal syndrome in suspects, or post-traumatic stress disorder (PTSD) in war veterans.

## Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a complex psychological disorder which develops in the aftermath of severe and/or life-threatening trauma (coma, burns, sexual abuse). Functional imaging in PTSD is in its infancy, but the body of evidence is growing, and through these insights PTSD has changed from "traumatic neurosis" to a biologically based psychological disorder. This anxiety disorder is most likely associated with changes in neural circuitry involving the frontal and limbic systems. The altered metabolism in these brain structures after a traumatic event is correlated to PTSD. Developments in the field of neuroimaging have allowed researchers to look at the structural and functional properties of the brain in PTSD [66].

Neuroimaging studies are usually performed as emotional activation studies, utilising e.g. combat-related sounds, images of a great fire, etc. [67, 68]; therefore, such studies are sometimes difficult to perform for ethical reasons.

Emotional activation studies demonstrate flow/metabolic activation most frequently in the precentral gyrus, posterior cingulate, amygdala and cerebellum, while deactivation is seen in the middle temporal gyrus, and inferior and middle frontal and parietal region.

Preliminary data show the circuits in the brain connecting regions of the medial prefrontal, medial temporal, frontal and parietal cortices. The future of such studies will probably help in understanding what makes some people more vulnerable to PTSD and how treatment influences and predicts the changes we see in brain imaging studies.

## Brain function during hypnosis

Hypnosis may be defined as a state of focused attention, concentration and inner absorption with a relative suspension of peripheral awareness.

PET studies demonstrated a vast activation in the occipital parietal, precentral prefrontal and cingulate cortex. This suggests that the hypnotic state does not rely on simple evocation of episodic memory but a reminiscence of mental imagery [69].

PET studies have given neuroimaging support for the nociceptive effect of hypnosis; the hypnotic state significantly enhances

the functional modulation between the midcingulate cortex and the large neural network involved in sensory, affective, cognitive and behavioural aspects of nociception [70]. In fibromyalgic patients under hypnosis, the cerebral blood-flow was bilaterally increased in the orbitofrontal and subcallosal cingulate cortices, the right thalamus and the left inferior parietal cortex, and was decreased bilaterally in the cingulate cortex. The observed blood-flow pattern supports notions of a multifactorial nature of hypnotic analgesia, with interplay between cortical and subcortical brain dynamics [71].

### **Impulsive aggression and suicidal behaviour**

Impulsive aggressive behaviour including deliberate self-harm and impulsive aggression towards others as well as suicidal behaviour is a major problem in healthcare. It is believed that its anatomical correlates are the prefrontal and temporal limbic regions and serotonergic dysfunction plays a crucial role.

In impulsivity, PET studies indicate that the impulsivity and chronic stress are associated with amphetamine-induced striatal dopamine release. In PET studies with high specific activity, [<sup>11</sup>C] raclopride was associated with blunted right ventral striatal DA release. Dopamine release was greater in low vs. high impulsivity subjects under conditions of low or moderate stress [72].

In suicidal behaviour, direct *in vivo* functional imaging with PET or SPECT demonstrated a reduction in the 5-HT<sub>2A</sub> binding index in suicide attempts by anxious and depressed suicide attempters and an increase in 5-HT<sub>2A</sub> binding in impulsive suicide attempters [73]. The importance of such studies is two-fold: first this may increase insight into the pathophysiology of impulsive aggression; secondly this may enable the development of new pharmacological approaches.

### **Hysteria and catatonia**

#### ***Hysteria (conversion disorder)***

The neural concomitants of hysteria and catatonia remain largely unknown. Hysteria, or conversion disorder, is defined as a psychiatric illness the symptoms or deficits of which, affecting voluntary motor or sensory function, cannot be explained by a neurological or general medical condition.

Functional neuroimaging has revealed selective decreases in the activity of frontal and subcortical circuits involved in motor control during hysterical paralysis, decreases in somatosensory cortices during hysterical anaesthesia, or decreases in the visual cortex during hysterical blindness [74]. The inhibition of normal neural networks seem to also be a common marker to tunnel vision or hysterical deafness.

#### ***Catatonia***

In catatonic patients, SPECT and PET studies showed dysfunctions of prefrontal and parietal cortices that possibly account for its motor, affective and behavioural disorders. Dysfunctions in the prefrontal cortex could account for some affective disturbances found in catatonia, whereas dysfunction in parietal lobes might participate in the disturbances of executive task planning.

In akinetic catatonia, SPECT and PET studies showed dysfunctions of the medial, prefrontal cortex, lateral parietal cortex and precuneus, which are known to be involved in conscious awareness [75].

The studies mentioned support the argument for the existence of a neural network of conscious awareness that may be disturbed in patients with stuporous catatonia.

### **Sleep disorders**

One-third of our lives are occupied by sleep. The utilization of nuclear medicine in sleep disorders is still in its infancy; this may be, however, a promising area for future development.

In healthy sleep there is an increase in function in the limbic and anterior paralimbic cortex in REM sleep and a decrease in the function of the higher cortical regions in known thalamocortical networks during NMREM sleep. Serotonin 5HT<sub>1A</sub> receptor PET studies showed a significant increase in their ligand-[<sup>18</sup>F]MPPF binding in sleep compared to wakefulness in the whole brain and all regions of interest examined: temporal cortex, mesial temporal region and cingulate cortex [76].

There is a collection of papers on diverse sleep disorders such as: sleep deprivation, insomnia, dyssomnia, narcolepsy, sleep apnoea and sleepwalking.

Perfusion abnormalities in patients with REM behaviour disorder are located in the brainstem, striatum and cortex. These abnormalities are consistent with the anatomic metabolic profile of Parkinson's disease [77].

In primary insomnia a pattern of hypoperfusion in the frontal medial, occipital and parietal cortices was found with particular deactivation in the basal ganglia [78].

In narcolepsy SPM analysis of the brain, SPECT showed hypoperfusion of the bilateral anterior hypothalami, caudate nuclei, and pulvinar nuclei of the thalami, parts of the dorsolateral/ventromedial prefrontal cortices, parahippocampal gyri and cingulate gyri in narcoleptics, as well as reduced cerebral perfusion in subcortical structures and cortical areas in narcoleptics. The distribution of abnormal cerebral perfusion is concordant with the pathway of the cerebral hypocretin system and may explain the characteristic features of narcolepsy, i.e. cataplexy, emotional lability and attention deficit [79].

In sleepwalking, activation of thalamocingulate pathways and persisting deactivation of other thalamocortical arousal systems was found [80].

### **Conclusions**

As shown above, there are few practical applications of nuclear medicine due to low specificity and low spatial resolution, although in the aspect of functional imaging it is still superior to CT/MRI, even in their functional modalities.

On the other hand, its investigational potential is still growing, as there is no imaging technique in sight which could replace metabolic and receptor studies, and also because the scope of functional imaging in psychiatric diseases is spreading from its traditional applications, like dementia or depression, towards many poorly investigated fields e.g. hypnosis, suicidal behaviour or sleep disorders.

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