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Neuropsychopharmacology 2

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Edited by
W. E. Bunney, Jr., H. Hippius, G. Laakmann
and M. Schmauß

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W. E. Bunney, Jr., M. D.
Professor of Psychiatry
College of Medicine
University of California at Irvine
Irvine, CA 92717, USA

Professor Dr. Hanns Hippius
Professor Dr. Gregor Laakmann
Psychiatrische Klinik und Poliklinik
der Universität München
Nußbaumstraße 7
8000 München 2, FRG

Priv. Doz. Dr. Max Schmauss
Bezirkskrankenhaus Augsburg
Dr.-Mack-Straße 1
8900 Augsburg, FRG

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Strategies for In Vivo Quantification of Human Neuroreceptors by Positron Emission Tomography *

D. F. WONG and L. T. YOUNG[1]

Introduction

At the present time, a number of groups of investigators are studying neuroreceptors and neurotransmitter systems with positron emission tomography (PET). In vivo quantification of neuroreceptors has been accomplished only in the past decade, and techniques are therefore still undergoing modification and validation. One of the earliest findings suggested a decline in the density of central dopamine D_2 neuroreceptors with age and different slopes of density versus age for men and women (Wong et al. 1984). Although there has been a steady improvement in imaging methods, controversy has surrounded many of the findings obtained with these techniques. Nevertheless, potential findings in neuropsychiatric illnesses at least stimulate future investigation and may, more optimistically, provide real insight into pathophysiology.

Abnormalities in neuroreceptor binding (and in some cases neuroreceptor densities) have been demonstrated in a number of neuropsychiatric disorders including schizophrenia (Wong et al. 1986c; Farde et al. 1987), temporal lobe epilepsy (Frost et al. 1988), poststroke depression (Mayberg et al. 1988), bipolar affective disorder (Wong et al. 1988), and Tourette's syndrome (Wong et al. 1988). The complexity and novelty of PET neuroreceptor imaging procedures indicate that improvements are still needed, and that the reliability of results obtained with such techniques may be questioned.

Very recently, two studies of drug-naive schizophrenics using different radiologands, PET techniques, and patient populations had markedly different results. One study completed in 1986 at the Johns Hopkins Medical Institutions in Baltimore (Wong et al. 1986c) demonstrated an approximately twofold elevation in D_2 receptor density (B_{max}) in ten drug-naive schizophrenics and five drug-free schizophrenics as compared to 11 normal controls (Fig. 1) using the ligand [^{11}C]*N*-methylspiperone (NMSP). These elevated densities continue to be demonstrated in our sample, which has since been expanded to 20 drug-

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[1] Department of Radiology and Nuclear Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD, USA.

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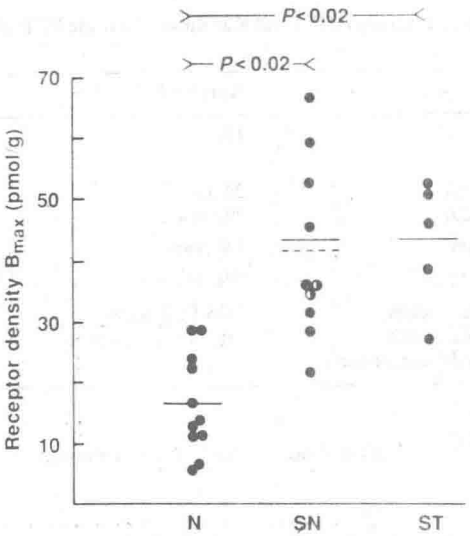

Fig. 1. Dopamine D_2 receptor density (B_{max}) in the caudate nucleus in normal volunteers (*N*) and in drugnaive (*SN*) and drug-treated (*ST*) schizophrenics. *Solid horizontal lines*, mean values in each group. For the drug-naive group this line is the value for the eight subjects who had only a single 7.5-mg dose of haloperidol before their second PET scan (43.3 ± 5.7 pmol/g). *Dotted line*, mean of all ten subjects, including the two who received more than a single dose of haloperidol before their second PET scan (average receptor density in this group, 41.7 ± 4.6 pmol/g). Mean receptor densities for the normal volunteers and the drug-treated group were 16.6 ± 2.5 and 43.3 ± 4.7 pmol/g, respectively. There was a significant difference (*t* test with Bonferroni correction for multiple inference) between either the eight or ten drug-naive or the drug-treated schizophrenics and the normal subjects. (From Wong et al. 1986c)

naive schizophrenics, with a continuation in these elevations (Tune et al. 1989; Wong et al. 1989a, c). In 1987, a Swedish group at the Karolinska Institute using PET with the radioligand [^{11}C]raclopride did not demonstrate significant differences in D_2 receptor density or affinity between 15 drug-naive schizophrenics and normal controls (Farde et al. 1987). It has become clear that there are many factors which might contribute to such markedly different findings (Table 1). For present purposes, these divergent results between two studies of the same neuroreceptor in the same disorder serve as an example to illustrate some important considerations regarding PET neuroreceptor imaging in living human brain.

It is of interest that a similar problem occurred in the study of patients at risk to develop Huntington's disease using the [^{18}F]2-deoxyglucose (FDG) technique to measure cerebral glucose metabolism. Although two studies showed reductions in caudate glucose metabolism in subjects at risk for Huntington's disease (Mazziotta et al. 1987; Hayden et al. 1987), a later study did not (Young et al. 1987). These results are surprising since patients in all

Table 1. Comparison of Johns Hopkins University (JHU) and Karolinska Institute PET D_2 dopamine receptor studies

	JHU [a]	Karolinska [b]
n	10	15
Age		
Patients	31.2±3.6	24.0±3.7
Controls	24.3±2.0	29.1±4.6
Duration of illness	4.7 years	1.9 years [c]
Ligand	[^{11}C]NMSP	[^{11}C]Raclopride
B_{max} determination	Two PET scans with Wolfe plot and model comparison	Two PET scans with Scatchard plot

[a] Wong et al. (1986a, c).
[b] Farde et al. (1987).
[c] At the time of the scan, one-half of the subjects had been ill for less than 6 months.

three studies met the same diagnostic criteria and were all studied in the same country. Significant differences are present in the methods of image analysis which may in part account for divergent findings. These results are of particular concern since measurement of cerebral glucose metabolism with FDG is probably the most well-established PET technique. Following a number of important methodological issues in the development and interpretation of PET, neuroreceptor studies are considered.

Methodological Issues

Patient and Control Population

Perhaps partly due to the complex technology associated with PET scanning, an important issue in interpreting studies which attempt to quantify neuroreceptors is often neglected: the patient and control populations. Diagnostic criteria and clinical characteristics of patients are fundamental in designing and interpreting clinical investigations, particularly in psychiatry which has few disease markers or definitive diagnostic tests. Schizophrenia is a chronic debilitating neuropsychiatric disease which usually begins in adolescence or early adulthood (Lehmann and Cancro 1985). There are widely varying clinical presentations, in addition to variable symptoms occurring at different stages of illness. There appears to be a heterogeneous population of patients as well as differences in the acute versus chronic stages of this disorder. It is plausible that neurochemical findings in schizophrenia may become more prominent at later stages of illness rather than at the onset of symptoms. This situation would be consistent with computed tomography scan abnormalities which were found to be more apparent in chronic versus acute schizophrenia (Luchins 1982).

Regarding the controversy over D_2 receptor findings in the Hopkins versus Karolinska studies (Table 1), patients in the study from Johns Hopkins were older (mean age 31 ± 4 years, $n = 10$) and had been ill for a longer time (4.7 years) compared with the Swedish patients (mean age 24 ± 4, $n = 15$; mean duration of illness, 1.9 years). If D_2 receptor changes occur at a later stage of illness, such clinical issues may be relevant. The duration of illness, time of scanning relative to the first episode, the presence or absence of psychotic features, premorbid personality traits, and predominant positive or negative symptoms are just some examples of potentially relevant factors which may be important in interpreting PET neuroreceptor imaging in schizophrenia. Generally, it can be stated that there are relevant issues which relate to typical clinical manifestations of a particular neuropsychiatric disorder which must be carefully considered in the design and interpretation of a PET study.

In addition to clinical issues in the patient group, attention must be directed towards selecting appropriate control groups. Matching on the basis of age sex is extremely important in the case of D_2 receptor imaging, in which a fall with age (Wong et al. 1984) in addition to sex differences was suggested and continues to be found with more sophisticated models (Wong et al. 1986a, c, 1988, 1989a, c). Moreover, socioeconomic status and level of education need also be considered. In practice, it is difficult to recruit subject groups matched on these variables for such complex procedures as PET neuroreceptor studies. Since an essential feature of schizophrenia is the presence of impairment in social functioning (American Psychiatric Association 1987), matching on socioeconomic status and level of education may not be an appropriate. It is not clear, however, how important these variables are in the design or interpretation of PET studies. Indeed, there are many other variables which may potentially confound experimental design. All need to be considered and subject groups matched on important variables.

Radioligand Pharmacology

Important initial considerations in choosing a PET strategy to quantify a neuroreceptor in vivo in human brain include pharmacologic parameters of the proposed radioligand, such as the kinetics and affinity of binding, selectivity, and specificity. In general, PET radioligands can be divided into two types, those which reach a quasi-equilibrium during the PET scan and those which do not. The first type of ligand, for example raclopride, is rapidly reversible and displays considerable dissociation during the time interval of the PET scan. In the latter group, because of the time frame of the PET scan which is based on the short half-life of typical radioisotopes (^{11}C, $t_{1/2} = 20$ min; ^{18}F, $t_{1/2} = 110$ min), these nonequilibrating ligands, such as NMSP, can be considered to bind "irreversibly" because of minimal dissociation from brain regions. Perhaps this binding parameter is the most important factor in the design and development of a model to quantify neuroreceptors with the particular PET radioligand. Specific modelling issues are addressed below.