Journal of Psychopharmacology
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J Psychopharmacol 2005 19: 488
DOI: 10.1177/0269881105056530

The online version of this article can be found at:
http://jop.sagepub.com/content/19/5/488

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On behalf of:
British Association for Psychopharmacology

Psychopharm

Journal of Psychopharmacology
19(5) (2005) 488–493

ISSN 0269-8811
SAGE Publications Ltd, London, Thousand Oaks, CA and New Delhi
10.1177/0269881105056530

The striatal dopamine transporter in first-episode, drug-naive schizophrenic patients: evaluation by the new SPECT-ligand [^{99m}Tc]TRODAT-1

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Abstract

Following the current hypothesis that acute schizophrenic psychotic illness is associated with a striatal 'hyperdopaminergic state', presynaptic integrity and dopamine transporter (DAT) density in first-episode, neuroleptic-naive schizophrenic patients was measured by single-photon-emission-tomography (SPECT) and compared with that in healthy control subjects. A new SPECT-ligand for assessment of the striatal DAT, the Technetium-^{99}m-labelled tropane TRODAT-1 ([^{99m}Tc]TRODAT-1), was used. Ten inpatients suffering from a first acute schizophrenic episode and 10 age- and sex-matched healthy control subjects underwent SPECT with [^{99m}Tc]TRODAT-1. On the day of SPECT, psychopathological ratings were performed with the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS) and Schedule for Assessment of Negative Symptoms (SANS). Patients had not previously received any neuroleptic or antidepressant medication. Mean specific TRODAT-1 binding in the striatum did not differ significantly between the patient and the age- and sex-matched control group (1.25 vs. 1.28). Variance was significantly higher in the patient group. The data obtained with the new ligand in first-episode, drug-naive schizophrenic patients are in line with the PET results from the group of Laakso *et al.* in a comparable patient sample. [^{99m}Tc]TRODAT-1 seems to be a valuable new SPECT-ligand in the evaluation of the presynaptic site of the striatal dopaminergic synapse in schizophrenia.

Keywords

schizophrenia, striatal dopamine transporter, first episode, drug-naive, SPECT, [^{99m}Tc]TRODAT-1

Introduction

The role of the dopaminergic system in schizophrenia is still a focus of discussion with regard to the etiology and pathogenesis of the disease. Certainly, connotation has changed since the time of the classical 'dopamine hypothesis of schizophrenia', once established based on the data from Carlsson (Carlsson and Lindqvist, 1963). Using dopamine depletion with α-methylparatyrosin, Abi-Dargham and colleagues recently demonstrated that occupancy of the postsynaptic striatal dopamine D_2 receptor, by endogenous dopamine is significantly higher in schizophrenic patients than in healthy controls (Abi-Dargham *et al.*, 2000). Together with data from in vivo imaging protocols analysing the presynaptic dopamine metabolism and release, e.g., the use of radiolabelled L-dopa or amphetamin stimulation (Reith *et al.*, 1994; Hietala *et al.*, 1995; Dao-Castellana *et al.*, 1997; Breier *et al.*, 1997, Laruelle *et al.*, 1997, Abi-Dargham *et al.*, 1998; Lindstrom *et al.*, 1999; Laruelle *et al.*, 1999), there is an increasing amount of evidence for a

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'hyperdopaminergic state' or at least severe disturbances of dopamine regulation in acute psychosis. However, the basic mechanism of this process is not yet fully understood.

Theoretical and experimental cellular and animal work has revealed that the presynaptic dopamine transporter (DAT) plays a key role in regulating the dopamine (DA) content in the synaptic cleft by transporting it into DA terminals, thereby gating signal transduction by controlling the effective concentration of the neurotransmitter available for postsynaptic receptor binding (Bannon *et al.*, 2000). The dopamine transporter is located on DA nerve terminals and, in general, serves as a marker of DA nerve integrity. DAT´s are expressed in a small number of neurons in the brain, mainly in striatum and nucleus accumbens, but also in the globus pallidus, cingulated cortex, olfactory tubercle, amygdala, and the midbrain (Ciliax *et al.*, 1995).

To date only a few imaging studies have dealt with the assessment of the striatal presynaptic dopamine transporter in schizophrenia, and the data are inconsistent. Laakso found no differences in binding of the PET-ligand [^{18}F]CFT in nine neuroleptic-naive schizophrenic patients compared to age-matched healthy controls (Laakso *et al.*, 2000). In contrast, the group demonstrated a significant decrease – compared to age-matched controls – of DAT-binding of the same ligand in a group of eight stable, medicated, chronic schizophrenic patients (Laakso *et al.*, 2001). Using the single-photon emission computed tomography (SPECT-) ligands [^{123}I]β-CIT and [^{123}I]FP-CIT, neither Laruelle nor Lavalaye found binding differences in neuroleptic-naive or treated patients of different ages (Laruelle *et al.*, 2000; Lavalaye *et al.*, 2001).

With respect to the inconsistency of the data, it is of especial interest to analyse DAT-binding in schizophrenic patients with a ligand that has different chracteristics than those of [^{18}F]CFT- or ^{123}I-labelled ones. Owing to its favourable imaging characteristics, broad availability and cost efficiency, Technetium-99m [^{99m}Tc] is the most-used radioisotope. Only recently, a tropane derivative, TRODAT-1 [Ethanethiol, 2-((2(((3-(4-chlorophenyl)-8-methyl-8-azabicyclo(3,2,1)oct-2-yl)methyl)(2-mercaptoethyl) amino) ethyl) amino, (1R-exo-exo))-], was successfully labelled with [^{99m}Tc] (Meegalla *et al.*, 1997, 1998). [^{99m}Tc]TRODAT-1 has been characterized as a reversible binding agent to the DAT (for rev, see Kung 2001). Valid biodistribution data and dosimetry of [^{99m}Tc]TRODAT-1 are available (Mozley *et al.*, 1998). Animal data show a sensitive binding behaviour of TRODAT-1 to the DAT, depending on the endogenous dopamine level: minor changes induced by low doses of L-dopa, y-hydroxybutyrolactone (GBL) or apomorphine did not change TRODAT-1 binding whereas a high L-dopa dose and d-amphetamine reduced TRODAT-1 binding significantly in a dose-dependent manner. Additionally, pre-blocking of the DAT by CFT or methylphenidate inhibited TRODAT-1 binding, also in a dose-dependent manner (Dresel *et al.*, 1998). In our laboratory, time activity measurement was performed analysing TRODAT-1 binding behaviour to frontal, occipital, cerebellar cortex and striatum within ten healthy volunteers (Fig. 1; La Fougère 2003). Additionally, a study in 17 patients suffering from attention deficit hyperactivity disorder (ADHD) before and after methylphenidate treatment was performed demonstrating the usefulness of [^{99m}Tc]TRODAT-1 to label specific changes in striatal DAT availability (Dresel *et al.*, 2000). In schizophrenic patients, a first study of Hsiao *et al.*, did not demonstrate a significant difference of TRODAT-1 binding compared to the control group (Hsiao *et al.*, 2003). Thus, [^{99m}Tc]TRODAT-1 is presumed to be a valid SPECT-ligand with high specifity for DAT imaging, but to have lower affinity than other SPECT-ligands such as β-CIT or FP-CIT. Although, TRODAT-1 measures may be sensitive to large increases in synaptic dopamine, these are unlikely to be seen

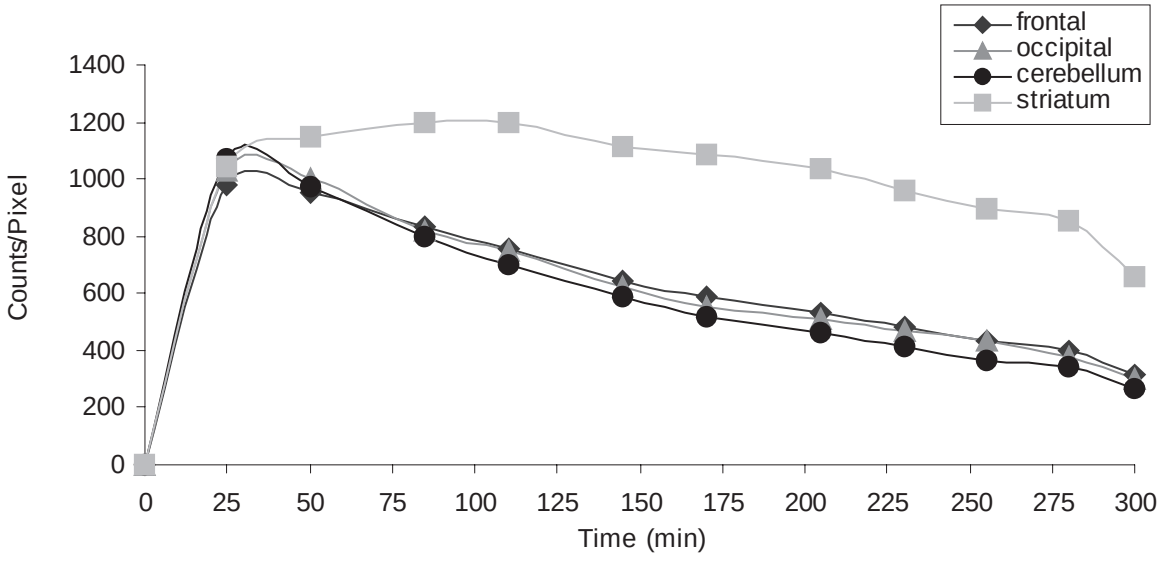

Figure 1 Time-activity curves of [^{99m}Tc]TRODAT-1 binding in 10 healthy volunteers; data from striatum and frontal, occipital and cerebellar cortex (adapted from La Fougère, 2003)

within schizophrenia considering the magnitude of change seen by other investigators.

The aim of the present SPECT investigation was to compare striatal DAT-binding of [^{99m}Tc]TRODAT-1 in first-episode, previously untreated patients with a diagnosis of schizophrenia and age- and sex-matched healthy controls.

Methods

The SPECT investigation was approved by the ethics committee of the LM-University of Munich, Germany and the local authorities of radiation protection. The study was performed in accordance with the ethical standards defined in the Declaration of Helsinki 1975, revised in Hong Kong 1989. Following a detailed description of the study, written informed consent was obtained from all subjects.

In this ongoing study, inpatients with a first diagnosis of paranoid schizophrenia according to DSM-IV/ICD-10 criteria were included in the first week after admission to hospital. In ten patients, diagnosis was confirmed by the independent psychiatrist responsible for the patient on ward after the end of treatment. Six males and four females, mean age 34.9 years (34.9 ± 12.11; range: 19 to 54), were included for analyses of the [^{99m}Tc]TRODAT-1-SPECT. The control group consisted of ten healthy subjects, six males and four females, mean age 37.8 years (37.8 ± 10.76; range: 21 to 53). On the day of SPECT, psychopathology ratings, including Clinical Gobla Impression (CGI), Global Assessment of Functioning (GAF), Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) and Schedule for Assessment of Negative Symptoms (SANS), were performed by an independent psychiatrist. Patients underwent a routine laboratory analysis, electrocardiogram (ECG) and structural magnetic resonance imaging (MRI). Concomitant medication was restricted to zopiclon.

SPECT scanning was typically performed in the morning. The procedure follows an established protocol (Dresel *et al.*, 2000, Krause *et al.*, 2000; La Fougère 2003). In brief, 180 minutes after radiotracer administration (740 MBq [^{99m}Tc]TRODAT-1), SPECT acquisitions were performed over a period of 50 minutes on a triple headed gamma camera (Picker, Cleveland, Ohio) equipped with high resolution fan beam collimators. The acquisition parameters included a 15% energy window centered on 140 keV, a rotational radius of 13 cm or less, 120 projection angles over 360 degrees, and a 128×128 matrix with a pixel width of 2.11 mm in the projection domain. The projection images were reconstructed by filtered back projection and filtered by a low pass filter. Chang's first order method was used for uniform attenuation correction. Images were uniformly resliced by drawing a line connecting the anterior-most aspect of the frontal pole to the posterior-most aspect of the occipital pole, which approximates the line connecting anterior and posterior commissures (AC–PC line).

In order to assess specific tracer uptake in the striatum, we used the region of interest (ROI) technique. In each patient, data were evaluated in the two consecutive transverse slices showing the highest tracer accumulation in the basal ganglia. The arithmetic mean of these two slices was calculated. Mean specific activity in the basal ganglia regions was calculated by subtracting the mean counts per pixel in the cerebellum as background (BKG) from the basal ganglia region (STR) and dividing the results by the mean counts per pixel in the background [(STR-BKG)/BKG]. Templates were used to define the striatal ROI's. The size and shape of the templates was established and optimized using the data from the control group ($n = 10$). For each individual patient, the templates were adjusted to fit and corrected for anatomical differences in angle, size and distance between the interesting structures using an individual structural MRI-scan by side. The non-specific background activity was estimated by drawing a ROI around the cerebellum. The operator was blind to the case. An example of a single case study using the [^{99m}Tc]TRODAT-1)-SPECT technique is shown in Fig. 2. Data were compared to the age-matched control group described above.

SPSS version 11.0 was used for statistical analysis of SPECT and sociodemographic data. Student's t-test was performed to compare two independent groups, i.e., patients vs. controls. The effect of the diagnosis (i.e., patients vs. healthy subjects) on TRODAT-1-ligand binding was studied with a one-way analysis of variance using age as the covariate (ANCOVA). Equality of variances were tested using Levene's test of equality of variances. Continuous values were correlated using Pearson correlation coefficients, whereby Spearman´s rho was calculated where necessary. Differences were considered to be significant when $p < 0.05$.

Results

There was no significant difference between the patient and control groups with respect to age (Students independent t-test

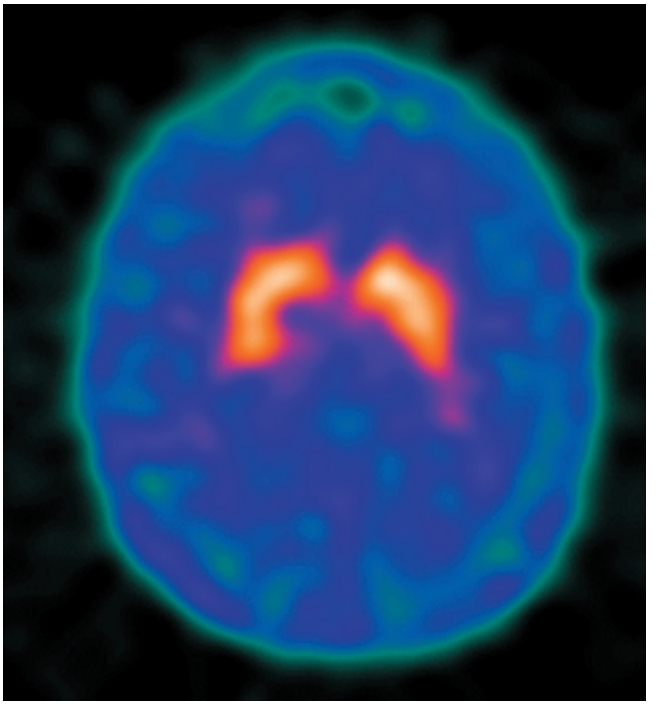

Figure 2 [^{99m}TC]TRODAT-1 binding, one drug-naive schizophrenic

Table 1 Patients' and healthy controls' demographic and specific TRODAT-1 binding characteristics

Patient	Gender m/f	Age (years)	ICD-10 diagnosis	Duration of illness (months)	[STR-BKG]/ BKG TRODAT-1	Healthy control person	Gender m/f	Age (years)	[STR-BKG]/ BKG TRODAT-1
1	m	19	F20.0	1	1.63	1	m	21	1.49
2	m	20	F20.1	6	1.17	2	m	28	1.30
3	m	26	F20.1	3	1.27	3	m	32	1.34
4	m	32	F20.0	8	1.52	4	m	33	1.26
5	f	32	F25.0	6	1.54	5	f	34	1.21
6	f	34	F20.0	9	1.28	6	f	36	1.20
7	m	35	F20.0	6	1.51	7	m	39	1.25
8	m	45	F25.0	4	0.73	8	m	49	1.26
9	f	52	F20.0	36	1.10	9	f	53	1.27
10	f	54	F20.0	18	0.71	10	f	53	1.19
Mean ± SD		34.9 ± 12.1		9.7 ± 10.3	1.25 ± 0.3			37.8 ± 10.7	1.28 ± 0.09G1

T value = −0.561, $p = 0.58$). Variance also did not differ significantly (Levene test F value = 0.052, $p = 0.82$). The mean duration of the patients´ illness was 9.7 ± 10.3 months. None of the patients had previously received neuroleptic or antidepressant treatment (see Table 1 for detailed description of patients and controls).

The mean striatal TRODAT-1-binding ((STR-CER)/CER) in the patient group was 1.25 ± 0.33, range 0.71 to 1.63, vs. 1.28 ± 0.09, range 1.19 to 1.49, in the control group. Patients showed no significant difference in [^{99m}Tc]TRODAT-1 binding to the striatal DAT compared to the control group (Students independent t-test T value = 0.29, $p = 0.78$). Variance of the ligand binding differed significantly (Levene test F value = 9.91, $p = 0.006$). (see Fig. 1: [^{99m}Tc]TRODAT-1-binding of patient 3).

The ANCOVA of TRODAT-1 binding comparing the diagnosis of both groups, with age as the covariate, showed a significant effect of age on TRODAT-1 binding (F value = 10.10, df 1, $p = 0.005$), but no significant interaction between age and diagnosis with respect to the ligand binding in either group (F value = 0.59, df = 1, $p = 0.452$). There was no significant gender effect, neither in the whole group (F value = 0.137, df = 1, $p = 0.72$) or in each of the two groups (F value = 0.00, df = 1, $p = 0.988$).

Analysis of the psychopathological assessment showed a mean CGI score of 6.45 (range 5.5 to 7), and a mean GAF score in the last year of 78 (range 90 to 60). Mean BPRS score was 73.2 (range 41 to 101), mean PANSS positive score 28.6 (range 21 to 39), mean PANSS negative score 25.2 (range 18 to 29), and mean PANSS global score 60.2 (range 38 to 77). In the SANSS, the mean score was 62.1 (range 35 to 86). There was no significant correlation between any of the psychopathological rating scales and the TRODAT-1-binding to the DAT.

As patients were admitted to hospital with a first diagnosis of a paranoid syndrome according to the DSM-IV/ICD-10 criteria for schizophrenia, we checked the diagnosis at the end of inpatient treatment. Six patients fulfilled the criteria for paranoid and two for disorganized psychosis and two were finally diagnosed as schizoaffectively ill.

Discussion

Our data in first episode, drug-naive schizophrenic patients are in line with the TRODAT-1-SPECT data in a comparable patient group by Hsiao (Hsiao *et al.*, 2003). The dopamine transporter SPECT studies in these patients performed with other ligands such as [^{123}I]β-CIT or [^{123}I]FP-CIT also found no difference in ligand binding compared to the control samples (Laruelle *et al.*, 2000; Lavalaye *et al.*, 2001). The PET data from Laakso *et al.*, who analysed nine neuroleptic-naive schizophrenic patients comparable to those in our group with respect to age and duration of illness, did not show significant overall binding differences, too (Laakso *et al.*, 2000).

Thus, the imaging data confirm the established *post mortem* results that there is no change of DAT density in schizophrenic patients (Bannon *et al.*, 2000), even though data from older and neuroleptic-treated patients may not be comparable with ours from first-episode and never-treated patients. Only a few post mortem studies have demonstrated a significant reduction of DAT in schizophrenic patients (e.g., Dean and Hussain, 2001). These studies used a different radioligand for DAT labelling compared to other groups which did not find this difference (e.g., Knable *et al.*, 1994). So, these results will certainly have to be discussed with special attention to methodological differences (Bannon *et al.*, 2001).

In an animal model of neonatal temporal limbic damage, which is supposed to mimic developmental defects equivalent to those postulated occurring in schizophrenia, Heinz and the group of Weinberger could not demonstrate a change in DAT availability to the SPECT ligand β-CIT, although postsynaptic D_2 receptor availability was significantly reduced (Heinz *et al.*, 1999). So, evidence is increasing, that there might be a striatal hyperdopaminergic state bound to illness phases in schizophrenia, which is not based on structural presynaptic defects, but may reflect a functional dysbalance.

Those imaging studies that found a difference in presynaptic dopamine activity in schizophrenic patients, e.g., after ampheta-

mine stimulation, obviously demonstrated a difference rather in function than in structural integrity as Laakso yet argued (Laakso *et al.*, 2000). Findings published recently by Laakso *et al.* reported a decrease of DAT-ligand binding in clinically stable, medicated, chronic schizophrenic patients. As the authors point out, these findings may have to be interpreted in the context of disease progression or neuroleptic medication (Laakso *et al.*, 2001). Contrarily, Sjoholm *et al.* showed just recently in likewise chronic, medicated schizophrenic patients, but in a small cohort (n = 6) and with the SPECT technique and β-CIT, a significant increase of DAT availability (Sjoholm *et al.*, 2004). Besides the methodological differences, there might be patient group differences regarding duration of disease, number, gender and neuroleptics used. In any case, schizophrenic patients seem to differ with respect to DAT availability at the beginning of disease compared to the chronic, medicated state.

We did not find a significant interaction between the binding of TRODAT-1 and one of the psychopathological ratings used. This may be due to the small size of the patient group analysed, however, it is in line with the two main imaging studies in this field by Laakso and Lavalaye mentioned above. Both studies had comparable sample sizes and neither detected significant correlations between binding to the DAT of the applied radioligand and the psychopathological rating scales.

An age-related decline of striatal DAT density has been described in healthy humans, although data from in vivo imaging studies differ with respect to characteristics and amount of the decline depending on the ligand used. With TRODAT-1, Mozley *et al.* found a nonlinear reduction of about 11% per decade until what they call a 'break point' at the age of 36 (±4). The decline is reduced to about 3% in later life (Mozley *et al.*, 1999). In our sample, we also found a significant influence of age on TRODAT-1-binding in both the patient and the age-matched healthy control group. We cannot reach a final conclusion about the degree of age-related vs. illness-related decline in our study due to the inhomogeneity of our patient group with respect to age – as this was not the primary interest of our study – and the sample size, which was too small to allow such a question to be answered. But we did not find an effect of diagnosis on TRODAT-1 binding in the patient group, so we may conclude that there is no illness specific change in DAT density.

A gender effect of dopamine transporter density has been described in animals (Rivest *et al.*, 1995). Female rats show a higher density of striatal DAT than males. In humans, a pronounced heterogeneity of striatal DAT in healthy females was found by Kuikka *et al.* (1997). In both our groups with six males and four females, we did not find a gender influence in the whole group or in the subgroups, respectively. This may happen by influence of the patient group – until now, sex differences with respect to DAT in schizophrenic patients have not yet described. And our group of healthy volunteers certainly is to small to detect the quite discrete differences found by other groups (e.g., Lavalaye *et al.*, 2000; Mozley *et al.*, 2001, Staley *et al.*, 2001).

Besides its binding characteristics, [^{99m}Tc]TRODAT-1 opens a further interesting field of SPECT technology: the labelling with the radioisotope [^{99m}Tc] offers the possibility to use simultaneously a second, iodine-123-labelled ligand in addition to [^{99m}Tc]. Dual-isotope SPECT studies of the DAT using [^{99m}Tc]TRODAT-1, with simultaneous assessment of the dopamine D_2 receptor using [^{123}I]IBZM, have already been performed in baboons (Dresel *et al.*, 1999). These studies showed that the simultaneously recorded images were comparable to those obtained on separate days. Recently, a group from Taiwan presented data using [^{99m}Tc]TRODAT-1 and [^{123}I]IBZM in a 6-hydroxydopamine (6-OHDA) animal model of Parkinson´s disease (Ma *et al.*, 2002). In monkeys, a significant reduction of TRODAT-1 binding in the lesioned compared to the healthy animals was shown, while the IBZM-binding to the D_2-receptor remained unchanged (Ma *et al.*, 2002). And finally, the first dual isotope human study in schizophrenic patients was published last year by Yang *et al.* (Yang *et al.*, 2004). Thus, it appears that a dual-isotope SPECT-technique to perform simultaneous assessment of the pre- and postsynaptic part of the dopaminergic synapse is available now. This technique will further increase the possibilities of research with respect to the measurement of interactions at the synaptic level in the normal state, in illness, and after functional stimulation, and the influence of specific treatment in humans in vivo.

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