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ORIGINAL PAPER

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Striatal dopamine transporter availability is associated with the productive psychotic state in first episode, drug-naive schizophrenic patients

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Abstract *Objective* Supposing a "hyperdopaminergic state" associated at least with acute psychotic illness phases in schizophrenia, a direct relationship between striatal dopamine metabolism and the core psychopathological symptoms rarely can be provided. Recently, a new SPECT ligand to the presynaptic dopamine transporter (DAT) was introduced. Association of DAT availability and the acute psychotic syndrome is now demonstrated in a large cohort of first episode, never treated schizophrenic patients. *Methods* Twenty-eight inpatients suffering from a first acute exacerbation of schizophrenia and 12 healthy control subjects underwent SPECT scanning with the new radioligand [^{99m}Tc]TRODAT-1. On the day of SPECT, psychopathology was assessed using specific scales including PANSS. *Results* There was no significant difference in [^{99m}Tc]TRODAT-1 specific binding to the striatal DAT comparing both groups. The extend of hallucinations was significantly inversely correlated with DAT availability in patients with a predominantly positive syndrome type. *Discussion* Our data support evidence that differences in presynaptic dopaminergic activity in schizophrenic patients are associated with the extend of the acute psychotic syndrome. [^{99m}Tc]TRODAT-1 seems to be a useful agent for *in vivo* assessment of a psychopathological association with dopamine metabolism.

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Introduction

The acute psychotic syndrome in schizophrenia is characterized by the core symptoms delusions, hallucinations, and thought disturbances. Neurotransmitter changes related to this symptom complex are supposed to involve an increase in dopaminergic transmission, a so-called "hyperdopaminergic state" (Carlsson et al. 2001). Using SPECT *in vivo* imaging, Marc Laruelle and his group were the first to demonstrate an increase of striatal dopamine transmission in schizophrenic patients suffering from an acute psychotic illness exacerbation which disappeared during remission (Laruelle et al. 1999). By different imaging protocols, e. g., the use of radiolabelled L-dopa or amphetamine stimulation, this increase of dopamine metabolism and release was demonstrated as a function of the presynaptic side of the dopamine synapse (Laruelle et al. 1997, 1999; Reith et al. 1994; Hietala et al. 1995; Dao-Castellana et al. 1997; Breier et al. 1997; Abi-Dargham et al. 1998; Lindstrom et al. 1999). Amphetamine stimulation induced a clear psychotic exacerbation in the patient groups, supporting vividly the idea of an involvement of the presynaptic dopaminergic neuron in productive psychotic states.

Dopamine transporter

The membrane bound presynaptic dopamine transporter (DAT) plays a key role in regulating the dopamine (DA) content in the synaptic cleft by transporting it into DA terminals. So, signal transduction is gated 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. DATs are expressed in a small

number of neurons in the brain, mainly in the striatum and nucleus accumbens, but also in the globus pallidus, cingulated cortex, olfactory tubercle, amygdala, and the midbrain (Ciliax et al. 1995).

Dopamine transporter imaging in schizophrenia

Specific neurotransmitter imaging, especially imaging of the membrane bound structures, deals with a complex interaction between the membrane bound structure itself, i. e., the DAT, the endogeneous ligand, i. e., dopamine, and the radioligand used. With respect to schizophrenia, the striatal DAT might be changed in number or in function and striatal endogeneous dopamine might be differentially regulated. In addition, affinity of the specific radioligand may be influenced by the illness specific, endogeneous neurotransmitter system changes. So, the availability of the DAT for binding of a specific radioligand can be influenced by a complex network of interactions.

To date only a few imaging studies have dealt with the assessment of the striatal DAT in acute psychotic states of schizophrenia, and the data are still relatively inconsistent (Laakso et al. 2000; Laruelle et al. 2000; Schmitt et al. 2000, 2005; Hsiao et al. 2003; Lavalaye 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. Laakso, by PET and the highly specific radioligand [^{18}F]CFT, could demonstrate a left-right difference in nine neuroleptic-naive schizophrenic patients compared to age-matched healthy controls.

[^{99m}Tc]TRODAT-1

With respect to the inconsistency of the imaging data, it is of especial interest to analyze DAT-binding in schizophrenic patients with a ligand that has different chracteristics than those of [^{18}F]CFT- or ^{123}I-labelled ligands. The 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))-], had been successfully labelled with [^{99m}Tc] and kinetic analyses had been performed (Meegalla et al. 1997, 1998; Mozley et al. 1998; for review see Kung 2001).

In animals, competition experiments with different substances acting directly at the DAT, i. e., amphetamine, or changing the synaptic dopamine content, i. e., L-dopa, had been performed (Dresel et al. 1998). It was demonstrated that TRODAT-1 binding specifically changes responding to synaptic endogeneous dopamine content.

In our laboratory, time activity measurement was performed analyzing TRODAT-1 binding behavior to frontal, occipital, cerebellar cortex, and striatum within 10 healthy volunteers (Fig. 1; la Fougère 2003). In addition, 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).

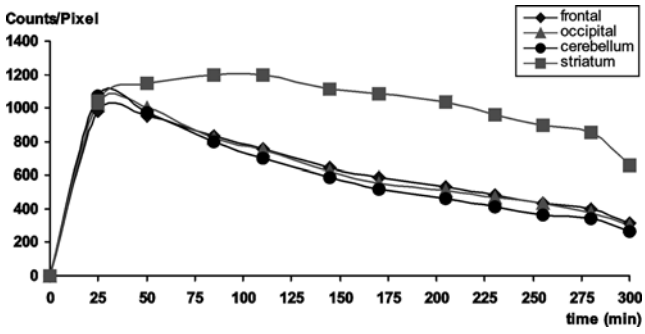

Fig. 1 Time-activity curves of [^{99m}Tc]TRODAT-1 binding in 10 healthy volunteers; data from striatum and frontal, occipital, and cerebellar cortex (adapted from la Fougère, 2003)

Using this new SPECT ligand we assessed no differences in DAT availability in a group of ten drug-naive, first-episode schizophrenic patients compared to an age-matched healthy control group (Schmitt et al. 2000, 2005). Hsiao recently confirmed our results in a group of eleven patients (Hsiao et al. 2003). Certainly because of the small sample size, no correlation between psychopathology and striatal DAT availability could be demonstrated by our both groups.

The aim of the present SPECT investigation was to compare striatal DAT-binding of [^{99m}Tc]TRODAT-1 in an enlarged cohort of first-episode, never-treated patients with a diagnosis of schizophrenia and a healthy control group and to analyze associations between striatal presynaptic dopamine metabolism and the core symptoms of the acute psychotic syndrome, namely delusions, thought disturbances, and hallucinations.

Methods

The SPECT investigation was approved by the ethics committee of the 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 Hong Kong 1989, and Somerset West 1996. Following a detailed description of the study, written informed consent was obtained.

Patients

A total of 43 inpatients with a diagnosis of a first acute psychotic episode indicating manifestation of schizophrenia according to DSM-IV/ICD-10 criteria were included in the first week after admission to the hospital. History of the first episode of psychotic symptoms and lack of psychopharmacological treatment was confirmed by the psychiatrist admitting, and by close relatives. Four patients did not complete the study: one withdrew permission before SPECT scanning, two were identified as having had neuroleptic treatment before, one had to be treated immediately because of severity of symptoms. Eleven patients were excluded from analysis because of a change of diagnosis during time on the ward. 28 patients (23 male, 5 female),

mean age 30.7 years (30.67 ± 8.90; range 19 to 54) underwent the complete study protocol. The control group consisted of 12 healthy subjects (10 male, 2 female), mean age 31.7 years (31.7 ± 8.41; range: 22 to 53).

Psychopathological ratings and clinical assessment

At the day of SPECT scanning, psychopathology ratings including Clinical Global Impression (CGI), Global Assessment of Functioning (GAF), and Positive And Negative Syndrome Scale (PANSS) were performed by a trained psychiatrist. Patients underwent a semistructural interview assessing sociodemographic data, a routine laboratory analysis, ECG, and structural MRI. Concomitant medication was restricted to zopiclon.

SPECT procedure

SPECT scanning was typically performed in the morning. The procedure follows our established laboratory protocol (Dresel et al. 2000; Krause et al. 2000; Schmitt et al. 2005). 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, the region of interest (ROI) technique was used. 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 ROIs. The size and shape of the templates was established and optimized using the data from the control group (n = 12). 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. Data were compared to the age-matched control group described above.

Statistics

SPSS version 12.0 was used for statistical analysis of SPECT and sociodemographic data. Student's t-test was performed to compare two independent groups, i. e., patients versus 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. The psychopathological syndrome type was calculated following the procedure of Kay by establishing the PANSS positive – PANSS negative difference: Patients with a positive syndrome type have a syndrome type value greater zero, patients with a negative syndrome type are characterized by a syndrome type value less than zero (Kay et al. 1987). The effect of the syndrome type on TRODAT-1 ligand binding was studied by using ANCOVA, too. 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

Patients' characteristics and control group

The patient group consisted of 23 men and 5 women, mean age 30.7 years (± 8.90, range 19–54). They were all right handed. None of the patients had ever received neuroleptic or antidepressant treatment before. As patients were admitted to the 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. Nineteen patients fulfilled the criteria for paranoid, six for disorganized, and three for undifferentiated psychosis (see Table 1 for description of patients data).

Analysis of the psychopathological assessment showed a mean clinical global impression score (CGI) of 6.45 (range 5 to 7; scaling 1–8), and a mean global assessment of function score in the last year (GAF) of 74.1 (range 90 to 40; scaling 100–0). Mean PANSS positive score was 30.0 (range 13 to 42; scaling 7–49), mean PANSS negative score 28.4 (range 18 to 44; scaling 7–49), and mean PANSS general psychopathology score 60.4 (range 34 to 78; scaling 16–112).

The control group was age matched with ten men and two women, mean age 31.7 (± 8.41; range 21.5 to 52.8). There was no significant difference between the patient and the control group with respect to age (Students independent t-test T value = –0.405, p = 0.69). Variance also did not differ significantly (Levene test F value = 0.134, p = 0.72).

Specific TRODAT-1 binding to the striatal DAT

The mean specific striatal TRODAT-1-binding [(STR-CER)/CER] in the patient group was 1.17 ± 0.22, range 0.71 to 1.63, and 1.19 ± 0.26, range 0.80 to 1.54, in the control group. Patients as a whole group 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 = –0.269, p = 0.79). Variance of the ligand binding also did not differ significantly (Levene test F value = 0.680, p = 0.41) (Fig. 2).

The ANCOVA of TRODAT-1 binding comparing the diagnosis of both groups, with age as the covariate, showed no significant effect of age on TRODAT-1 binding (F value = 2.804, df 1, p = 0.101), and no significant interaction between age and diagnosis with respect to the ligand binding in either group (F value = 0.142, df 1, p = 0.708), even if the age effect is more pronounced in the patient group (F value = 3.585, df 1, p = 0.068) compared to the control group (F value = 0.033, df 1, p = 0.859). There was no significant gender effect, neither in the whole group (F value = 0.232, df = 1, p = 0.632) nor in each of the two groups (F value = 0.051, df = 1, p = 0.822).

Table 1 Patients' age (years), gender (male = m, female = f), ICD-10 diagnosis, syndrome type according to PANSS, and TRODAT-1-specific binding values; [a] *s-type* syndrome type according to PANSS positive and negative score difference, *p* positive difference means positive syndrome type, *n* negative difference means negative syndrome type

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	mean
Age	37	19	26	35	31	33	34	24	24	37	34	19	40	26	35	32	27	35	52	26	37	31	26	28	20	19	19	54	**30.7**
Gender	f	m	m	m	m	m	f	m	m	m	m	m	m	m	f	m	m	m	f	m	m	m	m	m	m	m	m	f	
Diagnosis	F20.5	F20.0	F20.1	F20.0	F20.0	F20.0	F20.0	F20.0	F20.5	F20.0	F20.1	F20.1	F20.0	F20.1	F20.0	F20.0	F20.0	F20.0	F20.0	F20.0	F20.5	F20.0	F20.0	F20.0	F20.1	F20.1	F20.0	F20.0	
s-type[a]	n	p	p	p	p	n	p	p	n	p	n	n	p	p	p	p	p	p	p	n	n	n	p	p	n	n	p	p	
TRODAT-1	1.22	1.19	1.27	1.09	1.10	1.07	1.28	1.03	1.29	1.39	1.03	1.15	1.16	1.49	1.30	1.52	1.31	1.51	1.10	0.94	0.89	0.88	1.07	1.01	1.17	0.86	1.63	0.71	**1.17**

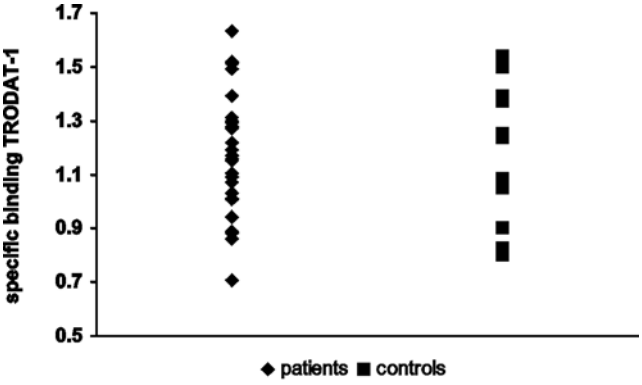

Fig. 2 Mean specific [^{99m}Tc]TRODAT-1 binding values [(STR-CER)/CER] to the striatal DAT in the patient and the healthy control group

Psychopathology and specific TRODAT-1-binding

By defining the psychopathological syndrome type at the day of SPECT using the PANSS positive – PANSS negative difference according to Kay (Kay et al. 1987), patients with a positive syndrome type (n = 18) showed a significant inverse correlation of DAT availability and the extent of hallucinations (Spearman-Rho = –0.609, p = 0.007; Fig. 3), a relationship which was not present in the negative syndrome type patients (n = 10) (Spearman-Rho = –0.312). This strong correlation was not found for the other core symptoms delusions (Spearman-Rho = –0.334) and thought disturbances (Spearman-Rho = 0.124). Specific TRODAT-1 binding values of both groups, the positive and the negative syndrome type, did not differ significantly to the healthy control group.

Discussion

DAT availability and psychopathology

With respect to the discussion about presynaptic changes at the striatal dopaminergic synapse in acute psychotic exacerbation in drug-naive, first episode

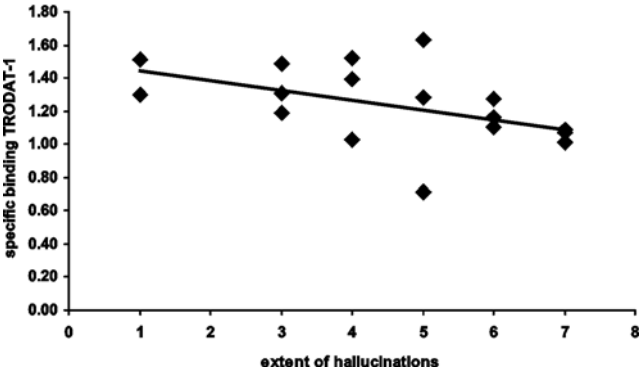

Fig. 3 Correlation of specific TRODAT-1 binding and extent of hallucinations in the positive syndrome type patients (n = 18): Spearman's Rho = –0.609, p = 0.007

schizophrenic patients, for the first time we present data about a relationship between striatal DAT availability and the type of psychotic syndrome. To our knowledge regarding the patient sample and the SPECT technique, this is the largest analysis in this field.

The clearest finding within the productive psychotic state is that the extent of hallucinations correlates significantly inversely with DAT availability in our group of 18 positive syndrome type patients according to Kay (Kay et al. 1987). Hallucinations, especially auditory verbal hallucinations, are present in an average of 60 % of schizophrenic patients and are a core symptom which often resists psychopharmacological treatment even if the patients are remitted with respect to other symptoms of the psychotic syndrome (Slade and Bentall 2002). During recent years, PET- and fMRI-studies have revealed a complex cortical network on the basis of inner speech and self-monitoring neural circuits which differs between schizophrenic patients with hallucinations, schizophrenic patients who never had hallucinations, and healthy control persons (Mc Guire et al. 1995, 1996; Silbersweig et al. 1995; Johns and McGuire 1999; Shergill et al. 2000a, b, 2003, 2004; Halligan and David 2001; Copolov et al. 2003; Hubl et al. 2004). Even if the data are inconsistent, what might be a function of methodological differences and sometimes quite small patient samples, the involvement of different brain regions including the striatum was found. The striatum showed increased activity associated with auditory verbal hallucinations (Silbersweig et al. 1995; Copolov et al. 2003). With respect to our data that hallucinations are associated with relatively low DAT availability which might reflect a high occupancy of the DAT by endogenous dopamine, this core symptom of psychosis may be a result of increased presynaptic dopaminergic metabolism. So, even if DAT availability in mixed groups of schizophrenic patients is not changed compared to healthy control persons, it might be associated with one of the core symptoms of the disease.

We did not find a significant interaction between DAT availability and the sum score of one of the psychopathological ratings used. This may no longer be due to the sample size, as was argued earlier by ourselves and other groups, when data of not more than around ten patients were presented. The studies of Hsiao, Laakso, and Lavalaye had those sample sizes and neither detected significant correlations between binding to the DAT of the applied radioligand and the psychopathological rating scales. One could argue that the psychopathological sum scores represent different neural functions which only in part affect striatal presynaptic dopamine metabolism.

DAT availability in first episode, drug-naive schizophrenic patients

Our data demonstrate no difference in striatal dopamine transporter availability between the whole group of never treated patients at the time of first exacerbation of psychosis and age-matched healthy controls. This confirms our earlier analysis with this technique in a group of ten patients (Schmitt et al. 2000, 2005). They are in line, too, with the data presented by Hsiao et al. (Hsiao et al. 2003) who did not find differences in overall striatal DAT availability using [^{99m}Tc]TRODAT-1 in 12 drug-naive schizophrenic patients.

These SPECT data follow the PET results of Laakso, who also could not demonstrate significant differences in binding of the specific PET-DAT ligand [^{18}F]CFT in nine neuroleptic-naive schizophrenic patients and an age-matched control group (Laakso et al. 2000). The nine patients of Laakso are comparable to ours with respect to age and severity of symptoms assessed by the PANSS. An analysis according to the psychopathological syndrome type was not performed, certainly because of the small number of the whole group. The dopamine transporter SPECT studies in schizophrenic 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).

DAT availability and the "hyperdopaminergic state"

Thus, the DAT imaging data confirm the established *post mortem* results that there is no change of DAT density in psychopathologically mixed groups of schizophrenic patients (Bannon et al. 2000). Naturally, data from older and neuroleptic-treated patients with a long history of the disease may not be comparable with ours from first-episode and never-treated patients. But, with our data available, there is additional reason to discuss those imaging studies that found a difference in presynaptic dopamine activity in schizophrenic patients, e. g., after amphetamine stimulation, with the interpretation of demonstrating a presynaptic difference rather in function than in structural integrity, as it was proposed by Laakso. Hallucinations as one of the core symptoms of schizophrenia seem to be strongly associated to presynaptic dopamine metabolism.

Use of [^{99m}Tc]TRODAT-1

With the data presented here, there is further evidence of the usefulness of [^{99m}Tc]TRODAT-1 for brain SPECT imaging at the striatal dopaminergic synapse. In addition, several groups could demonstrate the specificity of TRODAT-1 binding to the DAT in various neuropsychiatric disorders, e. g., Parkinson's disease or attention deficit hyperactivity disorder (ADHD) (Dresel et al. 2000; Mozley et al. 2000; Tzen et al. 2001; Kao et al. 2001; Krause et al. 2003). In ADHD, the effect of specific methylphenidate treatment could be measured by using TRODAT-1 (Krause et al. 2000; Dresel et al. 2000). With its high specificity to the dopamine transporter it seems

at least equivalent to the [^{123}I]-labeled ligands, without the high serotonin transporter affinity those show. Additionally, [^{99m}Tc]-labeled ligands present with numerous clinical advantages compared with ^{123}I-based radiopharmakons: [^{99m}Tc] is readily available, relatively inexpensive, and radiation exposure is lower than that of [^{123}I]-labeled compounds.

The labeling with the technetium-99m offers an additional interesting field of research: the possibility to use simultaneously a second, iodine-^{123}-labeled ligand. 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. 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. Such a 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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