Classification and Evaluation of the Pharmacodynamics of Psychotropic Drugs by Single-Lead Pharmaco-EEG, EEG Mapping and Tomography (LORETA)

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SUMMARY

Utilizing computer-assisted quantitative analyses of human scalp-recorded electroencephalogram (EEG) in combination with certain statistical procedures (quantitative pharmaco-EEG) and mapping techniques (pharmaco-EEG mapping), it is possible to classify psychotropic substances and objectively evaluate their bioavailability at the target organ: the human brain. Specifically, one may determine at an early stage of drug development whether a drug is effective on the central nervous system (CNS) compared with placebo, what its clinical efficacy will be like, at which dosage it acts, when it acts and the equipotent dosages of different galenic formulations. Pharmaco-EEG profiles and maps of neuroleptics, antidepressants, tranquilizers, hypnotics, psychostimulants and nootropics/cognition-enhancing drugs will be described in this paper. Methodological problems, as well as the relationships between acute and chronic drug effects, alterations in normal subjects and patients, CNS effects, therapeutic efficacy and pharmacokinetic and pharmacodynamic data will be discussed. In recent times, imaging of drug effects on the regional brain electrical activity of healthy subjects by means of EEG tomography such as low-resolution electromagnetic tomography (LORETA) has been used for identifying brain areas predominantly involved in psychopharmacological action. This will be demonstrated for the representative drugs of the four main psychopharmacological classes, such as 3 mg haloperidol for neuroleptics, 20 mg citalopram for antidepressants, 2 mg lorazepam for tranquilizers and 20 mg methylphenidate for psychostimulants. LORETA demonstrates that these psychopharmacological classes affect brain structures differently. © 2002 Prous Science. All rights reserved.

INTRODUCTION

As the target organ of psychotropic drugs is the human brain, the electroencephalogram (EEG) seems to be one of the best methods for classifying psychopharmacological agents and evaluating their pharmacodynamics. Specifically, it seems possible to objectively and quantitatively determine if, how, when and at which dosage a compound produces an effect on the human central nervous system (CNS). This has been demonstrated since the early days of the EEG by Berger (1), initially by eye-ball evaluation (2, 3), in the 1960s and 1970s by computer-assisted quantitative analysis of single leads (pharmaco-EEG) (4-10), and from the 1980s onwards by multilead analysis and subsequent mapping techniques (11-32).

In the last decade, EEG tomography techniques such as low-resolution brain electromagnetic tomography (LORETA) have been developed. LORETA computes a unique 3-dimensional electrical source distribution by assuming that the smoothest of all possible inverse solutions is the most plausible, which is consistent with the assumption that neighboring neurons are simultaneously and synchronously active (33, 34). Recently, Pascual-Marqui et al. presented a new implementation, introducing in addition to the smoothness constraint a neuroanatomical constraint (35). In this new version, the solution space is restricted to cortical gray matter and the hippocampus, as determined in the digitized Probability Atlas (Brain Imaging Center, Montreal Neurologic Institute) based on the Talairach human brain atlas. Thus, LORETA combines the high time resolution of the EEG with a source localization method that permits a truly three-dimensional tomography of the brain’s electrical activity, which makes it possible to answer questions on where a drug works within the brain.
Pharmacodynamics may be investigated in both normal volunteers and patients, and involves all phases of drug development (phase I-phase IV), i.e., from the first evaluation of effects on the normal human brain to therapeutic monitoring in patients. In the first instance, a target-oriented biometrical planning (maybe with the inclusion of a placebo control) and a target-oriented recording, evaluation, processing and interpretation of the data are requested. The requirements for such investigations have been described by many authors (6, 8-10, 14-16, 36-40) and are delineated in the Guidelines of the International Pharmaco-EEG Group (41, 42) and in its guidelines on statistical design and analysis for pharmacodynamic trials (45).

CLASSIFICATION OF PSYCHOTROPIC DRUGS

Representative drugs of the main psychopharmacological classes, such as neuroleptics, antidepressants, hypnotics, tranquilizers, nootropics/cognition-enhancing drugs and psychostimulants, induce (compared with placebo) significant changes in the quantitatively analyzed EEG, which (graphically displayed) result in different pharmaco-EEG profiles based on single-lead analysis (mostly O2-Cz) and pharmaco-EEG maps based on multilead analysis. The most typical profiles derived from numerous double-blind, placebo-controlled trials in our laboratory with over 130 different psychotropic substances are shown in Figure 1.
FIG. 1. Schematic pharmaco-EEG profiles of the main psychopharmacological classes. EEG variables are shown in the abscissae, differences between drug- and placebo-induced changes are indicated in the ordinates (in terms of t-values). The 0 line represents placebo. Low-potency sedative neuroleptics mainly induce an increase in theta and delta, a decrease in alpha and a slight increase in superimposed fast beta activities. In contrast, nonsedative high-potency neuroleptics mainly increase alpha and alpha-adjacent beta-1 activity. Thymoleptics of the amitriptyline type mainly produce an increase in theta, a decrease in alpha and an increase in superimposed fast beta activity, while thymeretics/thymoleptics of the desipramine type mainly enhance alpha activity. Anxiolytic sedatives, including hypnotics and tranquilizers, increase activity in all beta frequency bands and attenuate alpha activity, while only hypnotics augment slow activities. Nootropics/cognition enhancing drugs decrease delta and theta and increase alpha and alpha-adjacent beta activity, while psychostimulants mainly augment alpha and beta-1.

Pharmaco-EEG profiles and maps of neuroleptics

With neuroleptics, at least two major subtypes of pharmaco-EEG profiles may be differentiated after single-dose administration in normal subjects (Fig. 1). One seen after sedative neuroleptics (such as chlorpromazine, zotepine, zetidoline, clozapine and dapiprazole, which, apart from exhibiting their antidopaminergic effects also reveal antiserotonergic, antidiurenergic, anticholinergic and antihistaminic actions) is characterized by an increase in delta and theta activity, a decrease in alpha and, less consistently, an increase in concomitant fast beta activity. The other is observed after
nonsedative neuroleptics (such as haloperidol) and is characterized by a lack of delta augmentation and an increase in alpha and/or alpha-adjacent beta activity (17, 44, 45). As will be discussed later, these two pharmaco-EEG types may also be observed in schizophrenic patients after acute treatment. Single-dose administration of 100 mg fluperlapine, a sedative low-potency neuroleptic, resulted in a concomitant increase in delta/theta and beta activity, as well as a decrease in alpha activity, while 5 mg of the high-potency neuroleptic haloperidol produced opposite changes (46). In the early days of the pharmaco-EEG, different investigators described distinct profiles for different neuroleptics (8).

Pharmaco-EEG mapping after sedative neuroleptics, such as 50 mg chlorpromazine (47) or 30 mg chlorprothixene (16), demonstrated an attenuation of total power (1.3-35 Hz), an increase in absolute delta and theta power and a decrease in alpha and beta power. It also showed an increase in the relative power in the delta and theta and a decrease in the alpha and beta bands, as well as a slowing of the centroids of the delta/theta, alpha, beta and total power spectrum (Fig. 2). Galderisi et al. described the same findings after the sedative atypical neuroleptic clozapine (29). In contrast, the nonsedative neuroleptic 3 mg haloperidol, did not change total power, increased absolute and relative theta and beta power, slightly attenuated relative alpha power and left the centroids unchanged (Fig. 2). Thus, our pharmaco-EEG maps were in accordance with earlier pharmaco-EEG profiles based on single-lead recordings (O2-Cz). Certain discrepancies, for instance in regard to the increased beta activity observed after chlorpromazine in single-lead recordings (O2-Cz), could be resolved by the topograms, as the observed increase in beta activity was only found over the vertex (obviously due to sleep-related waves), whereas over all other brain regions there was a decrease.

EEG maps after single doses of 5 mg haloperidol in schizophrenics with a predominantly plus symptomatology did not demonstrate any changes in regard to absolute power and the centroid, while regarding relative power, an occipital delta/theta increase was seen (18). After 4 weeks of treatment with daily doses of 22 mg, there was an increase in total power as well as in absolute and relative power in

FIG. 2. Maps on EEG differences between nine representative drugs of the major psychopharmaceutical classes and placebo after acute oral drug administration (time of pharmacodynamic peak effect mostly 2 h postdrug). Statistical probability maps (SPM) depict intergroup differences in total power, absolute delta, theta, alpha-1, alpha-2, beta power; relative delta, theta, alpha-1, alpha-2, beta power and the centroids of the delta/theta, alpha, beta and total activity (from top to bottom) (bird's view, nose at the top, left ear left, right ear right, white dots indicate electrode positions). Orange, red and purple colors represent significant (p<0.10, 0.05 and 0.01, respectively) increases; dark green, light blue and dark blue indicate significant (p<0.10, 0.05 and 0.01, respectively) decreases as compared with normal controls. Different drug-induced changes are topographically displayed after single-dose administration of 50 mg chlorpromazine (n=15), 3 mg haloperidol (n=20), 75 mg imipramine (n=15), 20 mg citalopram (n=20), 20 mg d-amphetamine (n=15), 20 mg methylphenidate (n=20) and 400 mg pyritinol (n=15). While, for instance, 50 mg chlorpromazine decreases, 600 mg pyritinol increases total power. As can be seen, drugs of different psychopharmacological classes produce different pharmaco-EEG maps.
the delta/theta and alpha bands, while relative beta power and the centroid were significantly decreased. Single doses of 200 mg remoxipride induced an attenuation of total power and relative delta/theta power in the same patient type, as well as after 4 weeks of therapy with 400 mg daily, a further decrease in relative delta/theta power, as well as an acceleration of the centroid, predominantly frontotemporally. Thus, haloperidol revealed more sedative effects than the benzamide, which also was proven psychometrically. Recent studies with another benzamide, amisulpride, in relation to low doses of fluphenazine in minus symptomatology patients, showed after 2-mg fluphenazine a left occipitotemporal decrease in delta/theta activity and an acceleration of the centroid, and after 6 weeks, a decrease in delta/theta and an increase in alpha activity over many brain regions, together with a decrease in beta activity (48). Single doses of 50 mg amisulpride also induced a delta/theta decrease but an increase in beta activity and an acceleration of the centroid, which was also seen after chronic administration of 100 mg over 6 weeks. Thus, pharmaco-EEG maps demonstrate differences between different neuroleptics that are dependent upon the baseline as well as the type of patient, and last but not least, on the dosage. These differences may be important when it comes to selecting the right neuroleptic in the right dosage for the right patient. Schizophrenics with predominantly negative symptoms, for instance, found to be correlated with increased delta/theta activity (48), may respond better to nonsedative neuroleptics decreasing delta/theta activity, than to sedative neuroleptics increasing slow activity.

**Pharmaco-EEG profiles and maps of antidepressants**

With antidepressants, two main types of pharmaco-EEG profiles may be differentiated (Fig. 1): a thymoleptic (imipramine- or, amitriptyline-like) profile, showing a concomitant increase in slow and fast activities and a decrease in alpha activity (indicating sedative qualities) and a thymeric (desipramine-like) profile, mainly characterized by an alpha increase and a decrease in slow and fast activities (suggesting activating properties). Imipramine/amitriptyline-type changes were observed by us after doxepine, amitriptyline-N-oxide and antidepressants of the newer generation such as maprotiline, bimoclomol, danitrocimine and fluvoxamine (49-51). DMI-type pharmaco-EEG findings were observed after tranylcypromine (49), nomifensine (52), pirindol (53, 54), fluoxetine (55), zimelidine (56), sertraline (56), sercreloremine (57), moclobemide and diclofensine (58).

Pharmaco-EEG maps after sedative antidepressants, such as 75 mg imipramine, demonstrated an attenuation of total power as well as of absolute delta and theta and alpha power, mainly over anterior brain regions. There was also an increase in relative delta and theta and a decrease in alpha activity almost ubiquitously, while relative beta was reduced occipitally (Fig. 2). The delta/theta centroid became accelerated, the total centroid slowed over posterior regions. Similar findings, although with an increase in beta power, were described by us after venlafaxine, a neuronal uptake inhibitor of serotonin, noradrenaline and dopamine (in order of decreasing potency) (59). Ilil et al. described an increase in slow waves over frontal and temporal regions after 50 mg amitriptyline, while over occipital and parietal ones they observed a marked alpha decrease and an increase in concomitant beta activity, specifically over central areas (14). Herrmann and Schärer also described an increase in delta activity after 75 mg fluoxetine, reflecting a decrease in vigilance (60). Occipital alpha power decreased, beta-1 and beta-3 power increased, while absolute beta-2 power decreased.

In contrast, in our studies, nonsedative antidepressants, such as 20 mg of the SSRI citalopram, showed an attenuation of total power, a decrease in absolute delta, theta and alpha1 as well as an increase in beta power. There was also a decrease in relative theta and alpha1 and a pronounced increase in alpha2 and beta power, as well as a slowing of the delta/theta and an acceleration of the alpha, beta and total centroid (Fig. 2). Tianeptine, a new tricyclic antidepressant enhancing serotonin reuptake, showed slightly activating properties paralleled by a thymopsychic improvement in doses of 12.5 mg. A 25-mg dose produced an activation in the EEG up to the fourth hour and a sedation thereafter, accompanied by an initial improvement in the tymopsychic and differential changes (improved mood, decreased vigility), while the noopsyche was found improved at all times (23).

**Pharmaco-EEG profiles and maps of tranquillizers and hypnotics**

Anxiolytic sedatives comprise (according to WHO, 1967) both tranquillizers and hypnotics, as they have certain pharmacological properties in common. Indeed, they also share features in pharmaco-EEG profiles, as they all decrease total power and absolute and relative power of alpha activity, increase absolute and relative power of beta activity, accelerate the centroid and increase the centroid deviation of the total activity (Fig. 1). Differences between tranquillizers and hypnotics are predominantly observed in the slow activities. Daytime tranquillizers, such as oxazepam (61), prazepam (62), bromazepam (63) and clonazepam (64) do not induce augmentation of slow waves in the clinical dosage range, even if they are administered in extremely high doses with such as 75 and 150 mg prazepam (62, 65). Diazepam may also be counted in this group, although in the resting condition one may sometimes observe an increase in delta activity. This is of interest as diazepam is clinically used both as a daytime tranquillizer and as a sleep-inducing drug. On the other hand, there are benzodiazepines, which, in the low dosage range produce a tranquillizer profile, but in the higher dosage range a night-time tranquillizer (hypnotic) profile, increasing delta activity (Fig. 1). This was observed with the benzodiazepines brotizolam, lopizepam,
flurazepam (63, 66), flunitrazepam (67), triazolam (68), temazepam (64), cloxazolam (59) and lorazepam (63, 64).

Pharmaco-EEG maps confirmed this subclassification, as observed, for instance, after diazepam, clobazam, lorazepam and suriclone (70-73). Daytime tranquillizers, such as 30 mg clobazam, slightly attenuated total power, further decreased absolute and relative delta, theta and alpha, increased beta power, slowed the delta/theta and beta centroid and accelerated the total centroid (Fig. 2). Night-time tranquillizers, such as 2 mg lorazepam, markedly attenuated total power, augmented absolute delta and beta and decreased theta and alpha power, increased relative delta, theta and beta and decreased alpha power, further slowed the delta/theta centroid and accelerated the alpha and total centroid (the latter to a smaller extent than the daytime tranquillizer 30 mg clobazam) (Fig. 2). Frontal, central and parietal regions showed most prominent changes, as was noted also by other authors (14, 60). However, the serotonin-SHT$^{1A}$ agonist buspirone induced different types of changes, mainly characterized by an increase in theta power, an acceleration of the centroid of delta and theta power and no modification of alpha activity, but a slowing of its centroid and a tendency towards a reduction of beta activity, as well as a slowing of the centroid of the total activity (74).

Pharmaco-EEG profiles and maps of psychostimulants

Psychostimulants, such as d-amphetamine (75) and methamphetamine (76), but also pharmacologically unique wake-promoting agents, such as adrafinil and modafinil (77), induce pharmaco-EEG profiles predominantly characterized by an increase in alpha and alpha-adjacent beta activity, as well as by a tendency towards a decrease in slow and fast frequencies (Fig. 1). Contrasting reports in the literature seem to be due to differences in regard to baseline, dose and even recording conditions (resting EEG [R-EEG] vs. vigilance-controlled EEG [V-EEG]), which was observed in pharmaco-EEG mapping investigations (47); while in the V-EEG, total power tended to decrease after 20 mg d-amphetamine (Fig. 2), in the R-EEG it increased significantly. In the V-EEG, delta/theta power decreased and there was a similar tendency in the alpha power, while in the R-EEG, a significant decrease in delta/theta power, but increase in alpha power was noted. In the beta frequencies, absolute power remained unchanged in the V-EEG, while it was augmented in the R-EEG. The total centroid was always accelerated. Relative delta/theta power decreased specifically in the R-EEG, relative alpha activity generally remained unchanged in the V-EEG, but increased in the R-EEG, while relative beta power increased under both recording conditions. Differences to nootropics seem to lie in the total power, which was reduced after stimulants such as methylphenidate (Fig. 2) but rather increased after nootropics. This corresponds to the changes observed with antidepressants of the desimipramine type.

Caffeine (250 mg) induced only minimal changes in pharmaco-EEG maps, characterized by a decrease in total power and absolute power in the alpha and beta frequencies (16). The centroid showed a slowing over anterior brain regions, relative power generally remained unchanged. The most prominent finding was the acceleration of the alpha centroid, also reported by Etevenon et al. (78). Itil et al. described similar findings (14).

Pharmaco-EEG profiles and maps of nootropics or cognition-enhancing drugs

Nootropics or cognition-enhancing drugs generally decrease delta and theta and increase alpha and alpha-adjacent beta activity compared with placebo (Fig. 1). Drugs producing such a pharmaco-EEG profile belong to different chemical subclasses, such as co-deregicaine-mesilate and nicergoline of the ergot alkaloids (79, 80); vincamine; vinconate; SL 76100 and SL 76188 of the vincamine alkaloids and analogues (75, 81, 82); ilenprotil; tinfofedrine; sulocitil of the phenylethanolamines (83); piracetam; etiracetam; aniracetam of the pyrrolidine derivatives structurally related to gamma-aminobutyric acid (GABA) (84-88); ethophylline of the xanthine derivatives (85); butlfedrill (89); ouabain (g-strophantiane) of the cardiac glycosides; and acrhilline of the cardiac steroids. Further drugs inducing such CNS changes were pirodixilate (a glycolytic acid substitute pyridoxine) (90), Actovegin\textsuperscript{®} (a standardized deproteinized hemoderivative) (91), hexobendine and its combination with ethophylline and ethamivan (Instenon forte\textsuperscript{®}) (85, 92) and the calcium antagonist cinnarizine (8, 85).

These nootropic-induced changes are just opposite to EEG alterations in pathological aging (22) and reflect an improvement in vigilance. Vigilance is defined as the dynamic state of the total neuronal activity, which determines the availability and organization of man’s adaptive behavior (93). Pharmaco-EEG maps can demonstrate such changes even more impressively. As can be seen in Figures 1 and 2, 600 mg pyritinol augment total power, absolute alpha-1 and beta power and decreased alpha-2 power, decreased relative delta/theta and alpha-2 and increased relative alpha-1 power, while the centroid of the delta/theta and total power was accelerated and the alpha centroid slowed. Ergot alkaloids showed similar findings regarding absolute power and the centroid, as well as relative power in the delta/theta frequency, but showed a significant augmentation of relative beta activity (19). DUP 996 (linopirdine), a novel cholinergic drug, also increased total power and absolute alpha and alpha-adjacent beta power (20). Studies in patients with age-associated memory impairment, senile dementia of the Alzheimer type and multiinfarct dementia, as well as investigations with an experimentally induced
hypoxic hypoxioidosis in normal volunteers, support the above-mentioned findings of vigilance improvement (21, 22, 48, 73, 95-98).

PROBLEMS CONCERNING EEG CLASSIFICATION

Although the classification by pharmaco-EEG methods has been applied successfully even in drugs that had not been identified as psychoactive in animal pharmacology, one has to be aware of certain problems. The pharmaco-EEG profile itself seems to be influenced by three factors: i) the drug-specific effect; ii) drug-induced changes in vigilance; and iii) spontaneous fluctuations in vigilance.

This often explains the similarity between profiles of different psychopharmaceutical classes, specifically if one does not consider time-efficacy and dose-efficacy relations. One must further keep in mind that the method is basically empirical, and that data may be viewed from a different angle as their amount increases. It is of interest that certain antihistaminics, such as diphenhydramine, produce changes similar to those induced by antidepressants (AMH-type) (8). Thus, the question arises as to whether such antidepressant EEG profiles also indicate antihistaminergic or anticholinergic effects, which both drug groups have in common. This presumption has been confirmed by observations concerning yet another similar profile of a member of a different drug class, i.e., ketamine, a phencyclidine derivative, utilized as a dissociative anaesthetic (which is misused as a hallucinogenic drug and also has anticholinergic effects [99]) or clozapine, an anticholinergic neuroleptic drug. Thus, in classification attempts, it is important to consider dose-efficacy and time-efficacy relations, as well as recording conditions (e.g., vigilance-controlled vs. resting state). Moreover, the pretreatment state of the CNS seems to be an important variable.

TIME-EFFICACY RELATIONS

The time course of the cerebral bioavailability of a psychotropic drug at its target organ—the human brain—can impressively be demonstrated by changes in only one variable over time (Fig. 3) or based on multivariate statistics utilizing mapping of MANOVA and subsequent Hotelling T^2 test results (Fig. 4). In phase I studies, one has the possibility of objectively and quantitatively evaluating the onset, maximum and end of the central effect of a drug. These pharmacodynamic changes can be related to pharmacokinetic data (see below), but in patients, the evaluation of single-dose effects may provide valuable insight into the prognostic aspects of a planned treatment (e.g., beta decrease in schizophrenics, delta decrease in dementia patients).

DOSE-EFFICACY RELATIONS

Dose-efficacy relations can also be demonstrated on the basis of changes in single
variables, as seen in Figure 3, or based on multivariate techniques such as MANOVAs with subsequent Hotelling $T^2$ tests and mapping techniques (Fig. 4). By such means, one gains insight into the minimal centrally effective dose in man, which is important for later open and double-blind, placebo-controlled trials, in order to avoid complicated and frustrating investigations in patients. One may also obtain information on changes in CNS effects from certain dosage points onwards, as for instance the switch of CNS-activating to CNS-inhibitory effects after benzamides or the changes from a daytime to a night-time tranquilizer profile with benzodiazepines.

![Image](http://journals.prous.com/journals/servlet/xmlxsl/pk_journals.xml_article_pr?p_Journ...)

**Fig. 4.** Brain maps showing differences between drug-induced and placebo-induced central effects after 0.1 mg, 0.2 mg and 0.4 mg suriclone and 1 mg alprazolam (left to right column, respectively) at hours 1, 2, 3, 6, and 8 (top to bottom row). The vertex view shows nose on the top, occiput on the bottom, left ear to the left and right ear to the right. Electrode positions are indicated by white dots. Maps are based on Hotelling's $T^2$ obtained from multivariate tests in repeated measures ANOVA on the relative power of the nine frequency bands (In (power%/100-power%) transformations) for each electrode (R-EEG, n=15). The color key shows $T^2$ values with hot/red color indicating significant differences: larger than 2.96=$p$<0.10, larger than 4.1=$p$<0.05 and larger than 7.98=$p$<0.01. With increasing doses, suriclone exerts an increasing effect on the human brain compared with placebo, which may be observed topographically first over the vertex, right parietal and temporal regions. The encephalotropic effects of the single oral doses start as early as in the 1st hour and reach up to the 8th hour. The reference compound, 1 mg alprazolam, induces most CNS effects.

**BIOEQUIPOTENCY**

In a similar way as time- and dose-efficacy relations, the bioequipotency of an experimental compound can be explored and compared with that of a clinically well-known drug on the market. This is of special importance for determining the dosage in later clinical drug trials in patients. Without such calculations, the different intensity of the CNS effects of a drug in normal volunteers and patients would pose a great problem for predicting the optimal single and daily dosages for patients on the basis of phase I trials in normal volunteers. As can be seen in Figure 3, the equipotent dosage of the novel cloxazolam to the well-known 5 mg diazepam was found to be 2 mg, which would result in a dose relationship of cloxazolam:diazepam of 1:2.5 (8). In a subsequent double-blind, placebo-controlled clinical trial over 6 months in 15 generalized anxiety disorder patients, the psychiatrist could titrate the optimal dosage of diazepam and cloxazolam. The dosages found in the first, third and 24th week of treatment for the average, minimal and maximal daily dosage resulted in a dose equipotency of 1:2.5, which confirmed our pharmaco-EEG predictions (Fig. 3). In a similar way, the bioequipotency of different galenic formulations, such as a novel mixed micelle solution of diazepam vs. the standard formulation, can be determined (Fig. 5).
FIG. 5. Images of topographic differences in relative power changes of 16-20 Hz beta activity between two differently formulated drugs (mixed micelles vs. standard solution of diazepam 10 mg) given intravenously and intramuscularly (n=15; V-EEG: A12). While no significant differences between the two formulations could be observed after intravenous injection, the new mixed micelles solution was superior to the standard solution of diazepam in the 2nd and even in the 6th hour when given intramuscularly. The greater increase in beta activity over certain areas indicates a better absorption of the drug in the muscle.

THE RELATIONSHIPS BETWEEN PHARMACOKINETICS AND PHARMACODYNAMICS

When exploring pharmacokinetic/dynamic relationships, important information may be gained on the penetration of drugs through the blood-brain barrier to the site of the deep compartment receptor, on receptor binding, "hit-and-run" phenomena and active metabolites (52, 59). This is of particular interest if there is a time lag between plasma peaks and pharmacodynamic peak effects, such as that observed after the administration of nomifensine (Fig. 6). If one plots blood levels and EEG changes in the usual two-dimensional graphs for kinetic/dynamic comparison, a scatter appears, suggesting a lack of linear correlation. However, if one shows these points in their time sequence, a system appears in the scatter, resulting in a loop-shaped curve (hysteresis loop) (Fig. 7). This indicates that the maximal pharmacodynamic effect of nomifensine is not on the rising but on the descending slope of the kinetic curve. The larger the area within the loop, the greater the delay between changes in blood levels and CNS activity.
FIG. 6. Comparison between time-related changes in serum concentrations, EEG and psychometry after oral and intravenous nomifensine (n=10). Note the time lag between the blood level peak (1st to 2nd hour) and the maximum pharmacodynamic effect (6th hour).

FIG. 7. Relationship between nomifensine serum levels and total V-EEG changes after 75 mg nomifensine i.v. Numbers in circles refer to time of measurement (hours postadministration). A loop-shaped curve (hysteresis loop) indicates that the maximum pharmacodynamic effect is not on the rising but on the descending slope of the kinetic curve. The hysteresis loop depends upon the penetrability of the blood-brain barrier by psychotropic drugs and/or active metabolites.

By exploring pharmacokinetic/dynamic relations, we can also discover which of the investigated pharmacodynamic variables are the most sensitive for indicating drug effects and whether human behavior changes its type with increasing doses. When determining plasma concentrations after temazepam and flunitrazepam in ng/ml temazepam-equivalents by a radio receptor assay, peak plasma levels were observed after both drugs in the first hour, with a rapid decline after temazepam, while after flunitrazepam plasma levels decreased only slowly. Regression and correlation analyses between blood levels and EEG or psychometric changes after temazepam demonstrated that beta activity and the centroid of the EEG were positively correlated with plasma levels, while alpha activity as well as the psychometric variables attention, concentration, the alphabetical reaction test score, the Pauli test score, memory, psychomotor activity, complex reaction, reaction time, flicker frequency and skin conductance level were negatively correlated with plasma levels (Table 1). Based on the intercept, it can be concluded that EEG beta activity was the most sensitive variable, followed by the EEG centroid and EEG alpha activity. Psychometric variables started to deteriorate from a blood level of approximately 250 ng/ml upwards, while below this level an improvement may be expected. In fact, blood levels higher than 250 ng/ml were seen only after 40 mg temazepam in the first to the sixth hour and after 20 mg in the first and second hour. Our findings indicate that 20 and 40 mg temazepam exert sedative, sleep-inducing effects, while 10 mg show rather tranquilizing properties, which was confirmed by all-night polysomnographic studies in sleep-disturbed subjects (100, 101).
Maps on the correlation between plasma levels and EEG changes can also lead to a better understanding of the pharmacodynamic effect of a novel compound, as we demonstrated in a trial comparing CNS effects of a serotonin reuptake inhibiting drug, fluvoxamine, with those induced by the serotonin uptake enhancing compound tianeptine (23) (Fig. 8). The higher the tianeptine plasma level, the more pronounced were both absolute and relative powers in the beta frequency bands, mainly over frontotemporal regions. Furthermore, the higher the plasma levels, the faster the centroid and the higher the centroid deviation of the total activity. These findings indicate a more activating property in tianeptine in the highest dosage range investigated.

| Table 1: Response and correlation between blood levels and EEG as psychometric measures after tianeptine. (\*p<0.05, \*p<0.01, ***p<0.001). |
|-----------------|-----------------|-----------------|
| Blood levels   | Correlation coefficient | Response slope | Intercept (upward) |
| EEG-delta      | -0.65***         | 25.97           | 94.1             |
| EEG-sigma      | -0.47***         | -13.29          | 264.5            |
| EEG-frontal    | -0.38***         | 12.25           | 140.2            |
| Attention (ADHD) | -0.09**          | -0.67           | 116.7            |
| Concentration (AD, mean % Ra) | -0.20*** | -47.0           | 240.4            |
| Attention variability | -0.12*         | -0.57           | 254.4            |
| Alphabetic reaction test | -0.41***       | -5.79           | 230.9            |
| Alphabetic reaction test, tot | 0.12*         | 0.65            | 223.1            |
| Pupil test score | -0.40***         | -4.25           | 240.7            |
| Pupil test score% | 0.11           | 0.65            | 273.1            |
| Memory    | -0.29**         | -14.37          | 239.1            |
| Reaction time (total) | -0.23**   | -4.02           | 223.1            |
| Reaction time (correct) | -0.40***       | -5.05           | 239.5            |
| Reaction time (correct) | -0.22         | -0.57           | 250.0            |
| Reaction time (correct) | 0.12         | 20.84           | 251.7            |
| CPT      | -0.25**         | -12.16          | 251.4            |
| Anterior cingulum | 0.04         | 2.98            | 251.9            |
| Mood (VAS) | -0.03          | -0.37           | 255.9            |
| Affect    | -0.03          | -2.80           | 255.2            |
| Sociability | -0.29          | -5.79           | 295.2            |

FIG. 8. Correlation maps between changes in the EEG and the concentration of tianeptine in human plasma. Each of the 36 maps shows the topographic image of correlation coefficients between the tianeptine plasma level and a specific EEG variable. The upper part of the figure shows 13 correlation maps of absolute power variables, the
middle part of 12 relative power variables and the lower part of 11 centroid and dominant frequency measures. The 9-color key represents positive (hot/red colors) and negative (cold/blue colors) correlation coefficients. Significance levels are shown in the insert. The higher the tianeptine plasma level, the more pronounced is both absolute and relative power in the beta frequency bands, mostly over the fronto-temporal regions. Furthermore, the higher the plasma levels, the faster the centroid and the higher the centroid deviations of the total activity.

**ACUTE VERSUS CHRONIC EFFECT, CHANGES IN NORMAL SUBJECTS AND PATIENTS**

In contrast to the abundant knowledge of acute drug effects on brain activity in normal subjects, there is a lack of data concerning chronic CNS effects. The reason for this lies mainly in the side effects induced by neuroleptics and antidepressants. However, with the advent of a new generation of antidepressants, the possibility arose of studying compounds with a better tolerability over a longer period of time, even in normal subjects. After 2-week administration of pirlindol, a new noradrenaline uptake and monoamine oxidase (MAO) inhibitor, we found less effect than after acute dosing in normal subjects, which suggests adaptation phenomena (53). The latter are well documented at the receptor level (downregulation). After anxiolytics and nootropics, we found similar acute and chronic profiles, while after neuroleptics different changes were observed (46).

We found differences in CNS changes induced by a certain drug between normal volunteers and patients, which may be due not only to different sedation thresholds (68), but mainly to differences in brain function between untreated patients and normal subjects, which have been discussed in a separate paper (102).

**CNS EFFECTIVENESS AND THERAPEUTIC EFFICACY**

The relationship between drug-induced quantitative EEG changes and therapeutic efficacy can be considered from several points of view.

Some EEG changes are indicative of certain clinical alterations in subsequent clinical trials. There are numerous examples for this relationship in the pharmaco-EEG literature (6, 53, 68, 103). In this instance, the pharmaco-EEG can be seen as a predictive model in human pharmacology, not unlike the models in animal pharmacology. This applies if the drug-induced EEG changes in normal subjects are different from those in patients. This is often the case with EEG changes after nootropics, suggesting a vigilance improvement in both normally aging subjects and demented patients (104, 105).

Pharmaco-EEG changes are directly linked to behavioral alterations in both normal subjects and patients. In various studies we demonstrated that EEG alterations reflecting a vigilance improvement after acute drug administration in normal elderly subjects were similar to those observed in geriatric and organic brain syndrome patients, which in turn were associated with clinical improvement (16, 19, 90, 98, 105, 106).

Looking closely at the differences between nine major mental disorder patients and normal controls in 15 topographically displayed EEG measures and the pharmaco-EEG maps of the representatives of the major psychopharmacological classes, one may see that the differences between patients and normal controls are in certain instances opposite to the changes induced by the drugs compared with placebo. This fact speaks for a key-lock principle in diagnosis and psychopharmacological treatment of mental disorders, which has been discussed elsewhere (102). The differences between generalized anxiety disorder (GAD) patients and normal controls (26), for instance, are opposite to the changes induced by tranquillizers compared with placebo in both normal subjects (8, 61-66, 68, 73, 79) and patients (106) (Table 2).

| Table 2: EEG differences between normal volunteers (EEG) and psychiatric patients (EEG) in relation to changes after acute administration of individual psychopharmaceuticals (difference EEG normal vs. psychiatric patients) |
|------------------|------------------|
| **EEG variable** | **Differences**   | **Changemean activity (EEG)** |
|                  | **EEG normal**   | **EEG psychiatric** |
| Total power      | + + + + + + + + | + + + + + + + + |
| Absolute power   | + + + + + + + + | + + + + + + + + |
| Delta + Beta     | + + + + + + + + | + + + + + + + + |
| Alpha + Beta     | + + + + + + + + | + + + + + + + + |
| Beta + Alpha     | + + + + + + + + | + + + + + + + + |
| Deca + Sig          | + + + + + + + + | + + + + + + + + |
| Deca + Sig        | + + + + + + + + | + + + + + + + + |
| Contral + Sig      | + + + + + + + + | + + + + + + + + |

Finally, we found acute quantitative EEG changes to be of prognostic value regarding
subsequent therapeutic outcome: the greater the increase in average frequency 2 h
after the administration of single oral doses of 10 mg lorazepam, the more
pronounced the clinical improvement (Zung SAS score) in patients after 3 weeks of
chronic therapy.

PHARMACO-EEG IN THERAPEUTIC MONITORING

Quantitative EEG and brain mapping techniques can be utilized in therapeutic
monitoring of both an individual patient (Fig. 9) and a patient group (Fig. 10), and as
a prognostic indicator, as described for neuroleptic-induced EEG changes in
schizophrenics. Negative schizophrenia with increased delta/theta activities, for
instance, should respond better to neuroleptics decreasing slow activity than to those
increasing it (48).

FIG. 9. Brain maps of absolute delta power in a therapy-responsive and a therapy-resistant MID patient (left and
right columns, respectively) before (upper row) and after (middle row) 8 weeks of treatment with 20 mg nicergoline
daily as well as statistical probability maps (lower row). The color key represents absolute delta power in V² or p
values. While the therapy-responsive patient shows a decrease in slow activity (vigilance improvement), the
therapy-resistant patient shows an increase (vigilance deterioration).

FIG. 10. Maps on the effects of nicergoline (8 weeks, 2-30 mg/day; n=18) and placebo (n=22) on different EEG
frequency bands in MID patients. Changes in relative delta/theta, alpha-1, alpha-2 and beta power (top to bottom)
after nicergoline and placebo, compared with baseline, are shown in the left and middle column, respectively, inter
drug differences in the right column. The color key shows t-values; hot colors represent an increase (purple

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In the single case, therapy resistance is indicated by a lack of changes in the EEG after a certain dosage of a particular drug (Fig. 9). If a patient reacts to a drug clinically, he also shows changes in his EEG. However, it has to be stressed that differences to a control population, as for instance expressed in z-values, may still point out the patient as such. Group differences between therapy-responsive and -resistant patients have been described by us repeatedly (8).

Of course, there may also be different drug-induced changes in different nosological subgroups within a certain illness. As we showed with xanthoniloticinatae, there were differences in drug-induced changes, in regard to both type and locations in SDAT and MID patients (22). While SDAT patients showed, as the most characteristic change, an increase in slow alpha activity over frontal regions, MID patients showed a decrease in delta and theta activity and an increase in beta activity over fronto-polar regions.

Finally, several studies suggested that quantitative EEG changes after single doses are of prognostic value in regard to the therapeutic response of patients: the more pronounced the acceleration of the average frequency 2 h after one acute dose of loprazepam, the better the clinical and therapeutic response after 3 weeks of treatment (68).

IDENTIFYING BRAIN TARGETS OF PSYCHOTROPIC DRUGS BY EEG TOMOGRAPHY (LORETA)

Imaging of drug effects on regional brain electrical activity by means of EEG tomography in healthy subjects might be used for identifying brain areas predominantly involved in psychopharmacological action (108, 109).

In a recent double-blind, placebo-controlled, cross-over design study, LORETA identified brain areas characterized by a change in electrical activity after single oral doses of representative drugs of four different psychopharmaceutical classes, i.e., neuroleptics (haloperidol), antidepressants (citalopram), tranquilizers (lorazepam) and psychostimulants (methylphenidate), compared with placebo.

METHODS

Subjects

Twenty normal volunteers (10 males, 10 females) aged 23-34 years, 18 right-handed, 2 left-handed, were included. The subjects were in good health, totally drug-free and nonsmokers. They received randomly at weekly intervals single oral doses of placebo, 3 mg haloperidol, 20 mg citalopram, 2 mg lorazepam and 20 mg methylphenidate. The study was performed in accordance with the relevant guidelines of the Declaration of Helsinki, 1964, as amended in Tokyo, 1975, Venice, 1983, Hong Kong, 1989, and Somerset West, 1996. The protocol was approved by the ethics committee of the University of Vienna, School of Medicine, and the General Hospital of Vienna.

Data acquisition and analysis

A 3-min vigilance controlled EEG and a 4-min resting EEG with eyes closed was recorded at hours 0, 1, 2, 4, 6 and 8. In addition to 19 EEG channels (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 referenced to averaged mastoid electrodes), vertical and horizontal electrooculograms (EOG) were recorded (time constant: 0.3 s; high frequency response: 35 Hz) and digitized one-line with a sampling frequency of 102.4 Hz. After minimization of ocular artifacts, automatic artifact identification and recomputation to average reference, spectral analysis was performed for artifact-free 5-sec epochs, resulting in a frequency resolution of 0.2 Hz. For each recording, six 5-sec epochs of artifact-free, vigilance-controlled EEG were included in the analysis. Because different EEG frequencies reflect different functions, data were digitally filtered into seven frequency bands according to Kubicki et al. (110): delta (1.5-6 Hz), theta (6-8 Hz), alpha-1 (8-10 Hz), alpha-2 (10-12 Hz), beta-1 (12-18 Hz), beta-2 (18-21 Hz) and beta-3 (21-30 Hz). Subsequently, LORETA was used to estimate the 3-dimensional intracerebral current density distribution. LORETA images represent the power in 2394 voxels with a spatial resolution of 7 mm (35).

Statistical evaluations

Paired-samples t-tests were computed for log-transformed LORETA power at each voxel to evaluate differences between drug- and placebo-induced changes at different hours. These voxel-by-voxel t-values were displayed as statistical parametric maps. A single null hypothesis was tested for 'omnibus' significance (111). The Talairach coordinates of the highest t-value were determined. If this t-value was significant (p<0.05), the number of neighboring voxels constituting a suprathreshold region with p<0.05 was calculated and tested for significance by means of a binomial test (112). If more than one nonconfluent suprathreshold region was found, Bonferroni correction was performed. On the basis of the Structure-Probability Maps Atlas (113), the number of significant voxels in each lobe (frontal, parietal, occipital, temporal, limbic...
and sublobar), gyrus, and Brodmann area of the left and the right hemisphere was computed separately for each suprathreshold region.

PHARMACO-EEG TOPOGRAPHY

Maps depicting differences between drug- and placebo-induced alterations in seven frequency bands according to Kubicki et al. (110) are shown for the pharmacodynamic peak effects, which for lorazepam and citalopram were in the sixth hour post drug, and for haloperidol and methylphenidate in the fourth hour post drug (Fig. 11). Lorazepam (2 mg) induced an increase in delta power, a decrease in theta, alpha and beta-1 power and an increase in fast beta power. In contrast, 3 mg haloperidol induced significant increases in delta, fast alpha and beta power. The main effect of 20 mg methylphenidate was an increase in fast alpha and a decrease in fast beta activity. After 20 mg citalopram, delta and alpha-1 power decreased, whereas alpha-2 and fast beta power increased. Thus, drugs of different pharmacological classes induced different pharmaco-EEG maps.

PHARMACO-EEG TOMOGRAPHY

The results of the voxel-by-voxel statistics showing differences between drug- and placebo-induced changes in current source density evaluated by LORETA are displayed as LORETA-images in Figures 12-15 for citalopram, methylphenidate, haloperidol and lorazepam, respectively. Table 3 summarizes the results of the omnibus significance test for the different drugs and frequency bands. For significant differences, the predominantly involved hemispheres and lobes are given.
ABSOLUTE THETA POWER (6-8 Hz)

\[ \text{t}_{\text{max}} = 1.50 \text{ (r.e.) in BA 21 (Middle Temporal Gyrus, Temporal Lobe)} \]

\[ \text{t-values} \]

\[ 1.0 \quad 0.5 \quad 0.0 \quad -0.5 \quad -1.0 \]

20mg CITALOPRAM vs. PLACERBO
(4HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE ALPHA-1 POWER (8-10 Hz)

\[ \text{t}_{\text{max}} = -1.98 (p<0.10) \text{ in BA 6 (Medial, Paracentral Lobule, Paracentral Frontal Lobes)} \]

\[ \text{t-values} \]

\[ 3.0 \quad 1.0 \quad 0.5 \quad -0.5 \quad -1.0 \]

20mg CITALOPRAM vs. PLACERBO
(4HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE ALPHA-2 POWER (10-12 Hz)

\[ \text{t}_{\text{max}} = 2.06 (p<0.05) \text{ in BA 32 (Right, Superior Temporal Gyrus, Parietal/Temporal Lobes)} \]

\[ \text{t-values} \]

\[ 3.0 \quad 1.5 \quad 0.5 \quad -0.5 \quad -1.5 \]

20mg CITALOPRAM vs. PLACERBO
(4HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE BETA-1 POWER (12-18 Hz)

\[ \text{t}_{\text{max}} = 3.01 (p<0.01) \text{ in BA 21 (Right, Superior Temporal Gyrus, Temporal Lobe)} \]

\[ \text{t-values} \]

\[ 3.0 \quad 1.5 \quad 0.5 \quad -0.5 \quad -1.5 \]

20mg CITALOPRAM vs. PLACERBO
(4HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE BETA-2 POWER (18-21 Hz)

\[ \text{t}_{\text{max}} = 3.66 (p<0.01) \text{ in BA 21 (Bilateral, Inferior Temporal Gyrus, Temporal Lobe)} \]

\[ \text{t-values} \]

\[ 3.7 \quad 1.5 \quad 0.5 \quad -0.5 \quad -1.5 \]
FIG. 12. Effect of 20 mg citalopram on brain electrical activity at the pharmacodynamic peak (6HR-PRE). Images are based on voxel-by-voxel t-values of differences between drug- and placebo-induced changes for delta and theta, alpha-1 and alpha-2, and beta-1, beta-2 and beta-3 frequency bands (n=20). Red colors indicate increases, blue colors decreases compared with placebo. Black arrows indicate the extreme t-value of a significant suprathreshold region. For the size of the suprathreshold region see Table 1. For each frequency band, axial, sagittal and coronal slices through the voxel of the extreme t-value at the (X,Y,Z)-Talairach coordinate are displayed. Structural anatomy is shown in gray scale. (L: left; R: right; A: anterior; P: posterior). Citalopram induces an increase in absolute delta power in BA4 of the left precentral gyrus, a significant increase in alpha-2 power in BA22 of the right superior temporal gyrus, an increase in beta-1 power in BA21 of the right superior temporal gyrus, an increase in beta-2 power bilaterally in BA20 of the inferior temporal gyrus and, most pronouncedy, an increase in beta-3 power, with the maximum bilaterally in BA6. The increase in alpha-2 and beta power reflects activating properties of the drug.

20mg METHYLPHENIDATE vs. PLACEBO
(4HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE DELTA POWER (1.5-6 Hz)

<table>
<thead>
<tr>
<th>t-values</th>
<th>2.8</th>
<th>1.9</th>
<th>0.9</th>
<th>0.0</th>
<th>-0.9</th>
<th>-1.9</th>
<th>-2.8</th>
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ABSOLUTE THETA POWER (6-8 Hz)

<table>
<thead>
<tr>
<th>t-values</th>
<th>2.8</th>
<th>1.9</th>
<th>0.9</th>
<th>0.0</th>
<th>-0.9</th>
<th>-1.9</th>
<th>-2.8</th>
</tr>
</thead>
</table>

ABSOLUTE ALPHA-1 POWER (8-10 Hz)

<table>
<thead>
<tr>
<th>t-values</th>
<th>2.8</th>
<th>1.9</th>
<th>0.9</th>
<th>0.0</th>
<th>-0.9</th>
<th>-1.9</th>
<th>-2.8</th>
</tr>
</thead>
</table>
FIG. 13: Effect of 20 mg methylphenidate on brain electrical activity at the pharmacodynamic peak (4HR-PRE). Images are based on voxel-by-voxel t-values of differences between drug- and placebo-induced changes for delta and theta, alpha-1 and alpha-2, and beta-1, beta-2 and beta-3 frequency bands (n=20). For a technical description of the images see Figure 12. Methylphenidate predominantly induces an alpha-2 augmentation in the right temporal and limbic lobe, but also left occipitally, temporally and parietally as well as a beta-1 attenuation left frontally and a delta augmentation in the right temporal, frontal, limbic and sublobar cortices.
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ABSOLUTE THETA POWER (6-8 Hz)

\[ t_{max} = 2.56 \, (p < 0.01) \] in BA 44 (Right, Inferior Parietal Lobule, Parietal Lobe)

\[ N_{min} = 43 \pm 11 \%

3mg HALOPERIDOL vs. PLACEBO
(4HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE ALPHA-1 POWER (8-10 Hz)

\[ t_{max} = 1.94 \, (p < 0.10) \] in BA 19 (Bilateral, Insula, Parietal Lobule, Sub-limbic)

ABSOLUTE ALPHA-2 POWER (10-12 Hz)

\[ t_{max} = 2.40 \, (p < 0.01) \] in BA 21 (Bilateral, Middle Temporal Gyrus, Temporal Lobe)

\[ N_{min} = 107 \pm 1 \%

3mg HALOPERIDOL vs. PLACEBO
(4HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE BETA-1 POWER (12-16 Hz)

\[ t_{max} = 5.48 \, (p < 0.01) \] in BA 6 (Medial Frontal Gyrus, Frontal Lobe)

\[ N_{min} = 157 \pm 21 \%

\[ t_{max} = 2.07 \, (p < 0.01) \] in BA 46 (Left Supramarginal Gyrus, Parietal Lobe)

\[ N_{min} = 85 \pm 18 \%

ABSOLUTE BETA-2 POWER (18-21 Hz)

\[ t_{max} = 4.10 \, (p < 0.01) \] in BA 45 (Left, Inferior Parietal Lobule, Parietal Lobe)

\[ N_{min} = 195 \pm 18 \%

\[ t_{max} = 2.04 \, (p < 0.01) \] in BA 31 (Medial Frontal Gyrus, Frontal Lobe)

\[ N_{min} = 195 \pm 18 \%
FIG. 14. Effect of 3 mg haloperidol on brain electrical activity at the pharmacodynamic peak (4HR-PRE). Images are based on voxel-by-voxel t-values of differences between drug- and placebo-induced changes for delta and theta, alpha-1 and alpha-2, and beta-1, beta-2 and beta-3 frequency bands (n=20). For a technical description of the images see Figure 12. Haloperidol induces a local increase in absolute delta power in the left BA20, followed by an increase in BA8, a local theta increase in the right BA40, but also left BA20 and medial BA6. The changes, however, do not reach the suprathreshold level. Haloperidol induces a bilateral alpha-2 augmentation in temporal regions, an increase in beta-1 power in BA6 and the left BA40, in beta-2 power in the left BA40 and medial BA31, and in beta-3 power in BA23 in the cingulate gyrus, thereby revealing an activating mode of action in low doses.

2mg LORAZEPAM vs. PLACEBO
(6HR-PRE, t-VALUES; V-EEG; N=20)

ABSOLUTE DELTA POWER (1.5-6 Hz)

ABSOLUTE THETA POWER (6-8 Hz)

ABSOLUTE ALPHA-1 POWER (8-10 Hz)
FIG. 15. Effect of 2 mg lorazepam on brain electrical activity at the pharmacodynamic peak (6HR-PRE). Images are based on voxel-by-voxel t-values of differences between drug- and placebo-induced changes for delta and theta, alpha-1 and alpha-2, and beta-1, beta-2 and beta-3 frequency bands (n=20). For a technical description of the images see Figure 12. Lorazepam decreases theta and alpha-1 power ubiquitously, with extremes seen in BA10 and 11 of the prefrontal cortex. Alpha-2 power is also widely attenuated, which becomes most evident in the left BA37. Beta-1, beta-2 and beta-3 power shows the most pronounced augmentation in BA6 and 5.

TABLE 1. Drug vs placebo-induced changes: small differences based on t-squared tests for each frequency band (n=20). Parameter: t-values (t_{max}) and the number of significant voxels (N_{max} out of 2314 voxels) are given. For significant drug vs placebo effects, N_{max} is printed in bold and the pharmacodynamically involved frequency (F) (medial, T - temporal, P - parietal) is given. L - left, R - right, BA = Brodmann area.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug vs Placebo</th>
<th>t_{max}</th>
<th>N_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td></td>
<td>-0.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Theta</td>
<td></td>
<td>-0.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Alpha-1</td>
<td></td>
<td>-0.5</td>
<td>10.3</td>
</tr>
<tr>
<td>Alpha-2</td>
<td></td>
<td>-0.2</td>
<td>0</td>
</tr>
<tr>
<td>Alpha-3</td>
<td></td>
<td>-0.1</td>
<td>0</td>
</tr>
<tr>
<td>Beta-1</td>
<td></td>
<td>-0.8</td>
<td>100</td>
</tr>
<tr>
<td>Beta-2</td>
<td></td>
<td>-0.6</td>
<td>30</td>
</tr>
<tr>
<td>Beta-3</td>
<td></td>
<td>-0.4</td>
<td>100</td>
</tr>
</tbody>
</table>

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Compared with placebo, drugs of different psychopharmacological classes, such as tranquilizers, neuroleptics, psychostimulants and antidepressants, induce—compared with placebo—different changes in quantitatively analyzed EEG target variables, such as delta, theta, alpha and beta activity, reflecting differential effects on inhibitory, normal and excitatory EEG activities. Excitingly, for the first time we were able to demonstrate on the basis of multichannel EEG recordings and LORETA that drugs of different psychopharmacological classes affect brain structures differently. For instance, the changes in fast alpha and beta power induced by the tranquilizer lorazepam predominantly involved brain regions in the left hemisphere, while those induced by the antidepressant citalopram were located in the right hemisphere.

Interestingly, drug-induced changes in the occipital lobe were only seen in the alpha frequency band, with the exception of theta activity after lorazepam, which affected all 3 bands. Drug-induced changes in the beta frequency bands predominantly involved voxels located in the frontal and limbic lobes. Finally, drug-induced changes in the delta frequency range were seen predominantly in the temporal lobe: a right temporal increase after methylphenidate and a left temporal increase after citalopram.

**LORETA IMAGES**

**Citalopram (antidepressant)**

After 20 mg citalopram p.o., LORETA delta power increased left temporally and frontally (Fig. 12), which had not been seen in the EEG topography (Fig. 11). Citalopram-induced increases in fast alpha and beta activities were predominantly observed in right frontotemporal cortical areas (Fig. 12).

In detail, our LORETA findings after 20 mg citalopram demonstrated a widely distributed increase in beta-2 power, reaching its maximum bilaterally in BA6, a region involved in motor function, an increase in beta-2 power, reaching its maximum bilaterally in BA20 of the inferior temporal gyrus, and in beta-1 power in the right BA21 of the superior temporal gyrus, followed by an alpha-2 augmentation in the right BA22. While BA22 constitutes the auditory association area, there are also projection fibers to area 21, the origin of the major portion of the bundle of Turk, which also receives projection fibers from area 20. The results of a predominantly right hemispheric increase in alpha-2 and beta-1 activity after 20 mg citalopram are in agreement with the postmortem neurochemical studies of Arato et al. (114), implying a higher 5HT turnover in the right nondominant affective hemisphere than in the left cognitive hemisphere (already reported by Flor-Henry [115]). Intravenous administration of clomipramine induced an increase in the P300 latency of auditory evoked potentials and a shift to the right in the distribution of the peak values, resulting in increased activity in the right hemisphere, possibly due to greater inhibition in the left hemisphere (116). The latter findings were in agreement with a LORETA increase in delta power in the left temporal, frontal and parietal region. Interestingly, these changes did not reach the level of statistical significance in our EEG mapping investigations, which even showed a right temporoparieto-frontal decrease in slow activity, as described by Lader et al. (117). The left temporal and frontal delta increase observed after citalopram was in agreement with a significantly reduced regional cerebral blood flow measured by SPECT in the anterior and lateral part of the left temporal cortex as well as the anterior, lateral and posterior part of the left midfrontal cortex, reported by Van der Linden et al. (118).

**Methylphenidate (psychostimulant)**

Methylphenidate (20 mg) p.o. induced a significant increase in LORETA delta power in the left prafrontal brain region and a significant decrease in LORETA beta-1 power in the left prefrontal cortex (Fig. 13). This is of interest because these drug effects had not been observed in the EEG mapping (Fig. 11). The increase in LORETA alpha-2 power, however, was in accordance with the EEG-mapping results.

In detail, methylphenidate induced a delta power increase in the right temporal, frontal, limbic and sublobar cortices, with the maximum seen in the right BA38 of the superior temporal gyrus. Absolute theta power showed a local decrease in BA22 of the right insula, constituting an auditory association area. There was an increase in alpha-2 power, suprathreshold region showing its maximum in BA21 of the right middle temporal gyrus and a second in BA19 of the left precuneus, the seat of vertical and oblique conjugate movements of automatic type. An increase in normal alpha activity in this region could explain improvement in the connection of area 19 to the frontal oculomotor center, the sensorimotor cortex and the auditory cortex by long association bundles. Absolute beta-1 power, however, decreased, with the extreme seen over BA10 of the prefrontal cortex. There was a local increase in beta-2 power in BA19 bilaterally in the precuneus and a local decrease in beta-3 power in BA23 belonging to the cingulate gyrus. Volkow et al. demonstrated that single doses of 0.5 mg/kg methylphenidate i.v. tended to decrease the metabolism, as measured by PET and [11 C] cocaine, while repeated doses (0.5 mg + 0.25 mg/kg) administered i.v. 90 min apart from each other increased it, with the differences reaching the level of statistical significance in the frontal, parietal and occipital cortices and the hippocampus (119). In our LORETA studies, deactivating properties were reflected by the aforementioned delta increase, while activating properties were reflected by an alpha-2 increase in the right temporal and limbic left occipital, temporal and parietal cortices.
Haloperidol (neuroleptic)

After 3 mg haloperidol p.o., delta power increased in the left temporal lobe (Fig. 14), but the changes did not reach statistical significance in the omnibus test and thus did not constitute a suprathreshold region. However, the haloperidol-induced increases in fast alpha-2, beta-1, beta-2 and beta-3 power were significant. Alpha-2 power increased symmetrically in the posterior brain region and beta power increased medially in the frontal lobe and cingulate gyrus, and laterally in the left parietotemporal lobe.

In detail, 3 mg haloperidol induced a local increase in delta power in the left BA20, which projects fibers into BA21, the origin of the major portion of the bundle of Turker. A second maximum was found in BA8, containing a large portion of the frontal oculomotor field for voluntary conjugate movements of the eyes and cephalalgia. Absolute theta power showed a maximum increase in the right BA40, a territory strongly linked with associative functions. A second maximum was seen in the left BA23 that this medial BA6. An increased BA6 showed a deficit of anterior-frontal delta activity, a deficit of anterior-left temporal normal theta and alpha activity, and an excess of right parietal excitatory beta activity. Prefrontal functions include executive supervisory and coordinative activity, whose inhibition by slow electrical activity would be expected to result in a generally decreased cooperativity. The latter has been shown in schizophrenia by functional imaging correlational studies (122-126) as increased independence of regional brain processes and increased dimensional complexity of electrical measures (123, 127, 128). Left temporal functions related to schizoprenic symptomatology include memory (recall and classification), emotional coordination and linguistic construction functions. Left temporal areas, where Pascual-Marqui et al. (35) described a decreased activity of the normal function type (e.g., theta and alpha activity), have repeatedly been found deficient in functional imaging studies (129). Finally, the right parietal region, showing an excess of excitatory beta activities, proved to be associated with disturbances of awareness of the disease (anosognosia), body schema (130), eye movements (131) and sustained attention (132).

When we investigated haloperidol-induced changes in the regions that in the investigations of Pascual-Marqui et al. (35) had shown the greatest aberrations, in the delta, theta and alpha frequency bands we intriguingly found changes opposite to those described by Pascual-Marqui et al. for schizophrenics as compared with controls (key-lock principle) (102). However, the increase in beta power may reflect activating properties of low doses of haloperidol in normal volunteers via presynaptic D2 receptor blockade, as described by us after 2 mg (44).

Lorazepam (anxiolytic)

After 2 mg lorazepam p.o., a decrease in theta and alpha-1 power was observed in all cortical brain regions. The majority of voxels constituting the suprathreshold region of alpha-2 power decreases after lorazepam were located in the left hemisphere. Moreover, changes in beta power were predominantly seen in the left frontal lobe (Fig. 15).

In detail, lorazepam 2 mg induced an ubiquitous decrease in theta and alpha-1 power, with voxel changes similar seen in BA10 and BA11 of the prefrontal cortex. The latter is involved in mnemonic functions and other higher cognitive functions related to personality, insight and foresight. By decreasing normal functional theta and alpha activity, subjects may be more detached from their anxiety-provoking problems and ambivalence. Alpha-2 power was also widely decreased, most pronounced in the left fusiform gyri located on the inferior surface of the brain, consisting of the visual association cortex. This region contains high-order visual association areas that mediate spatial vision and visual, mnemonic and attentional processes. Indeed, in earlier studies we measured a decline in attention in normal volunteers (64). Finally, 2 mg lorazepam decreased beta-2 and beta-3 activity, predominantly in the left-sided BA6 and 5, which are known to be involved in motor functions. An increase in beta spindles there may result in an improvement of aberrant psychomotor behavior in the patients, but may also explain the decrease in psychomotor performance in volunteers (64). The beta increase in frontal regions also confirms the LORETA findings of Nobuhara et al. (133). In a placebo-controlled, parallel-group design study in 32...
normal subjects, they described an increase in beta-1 and beta-2 activity in the frontal cortices, which reflects a binding of diazepam to benzodiazepine/GABA receptors that occur in high density in the frontal neocortex. However, benzodiazepine receptors are abundant in neocortical cerebral, cerebellar and limbic cortices (134) and thus it comes as no surprise that theta and alpha-1 activity was attenuated in all our LORETA regions. Utilizing PET and 18FDG, De Wit et al. described a reduced global metabolism after diazepam (135). In contrast, GAD patients were reported to have an increased relative glucose metabolism in the left occipital (BA17), right posterior temporal and right precentral regions (136). There was no evidence of an asymmetry in the metabolism in the parahippocampal region, as reported by Nordahl et al. (137), who by means of FDG showed higher values over the right than over the left side in 12 panic disorder patients, or earlier by Reiman et al. (138). In this context it is of interest that in our LORETA studies, theta reduction was highest in the left superior frontal gyrus ($t_{\text{MIN}}=-6.03, p<0.01$) and almost equally pronounced in both parahippocampal gyri ($t_{\text{MIN}}=-6.01, p<0.01$).

What makes our LORETA findings with lorazepam even more exciting is the fact that they were opposite to recently obtained LORETA differences between GAD patients and normal controls (102). GAD patients showed an increase in delta and theta (mainly occipitally), alpha-1 (frontally, occipitally), alpha-2 (frontally) and beta-2 power, while Somnium®, a combination of 1 mg lorazepam and 25 mg diphenhydramine, induced just the opposite changes compared with placebo 12 h after the evening dose on top of 4-week chronic administration. Last but not least, in recent correlation studies we found high correlations between the SAS score and left temporal theta activity, thereby confirming the observations by Tiihonen et al. of a decreased benzodiazepine receptor binding in the left temporal pole in GAD patients compared with healthy normal controls (139). As we also obtained HAMAS and SDS ratings, it is noteworthy to mention that HAMAS ratings were not correlated with LORETA findings, while the highest correlation coefficients were seen between SDS ratings and delta power in the left temporal lobe (+0.58, involving 1713 voxels) and theta power in the left temporal (+0.46), left frontal (+0.45) and right frontal (+0.41) lobes. This confirms recent findings of Conca et al. (140), correlating ratings in depressed patients with FDG and HMPAO SPECT findings. They described that patients with low anxiety scores demonstrated a marked dynamic coupling bilaterally for the superior temporal gyrus, while patients with high anxiety scores showed statistically significant correlations to regional cerebral blood flow and regional cerebral glucose metabolic rate only in the left superior temporal gyrus. Buchsbaum et al. (141) and Matthew and Wilson (142) described that clorazepate and diazepam decreased anxiety and also cerebral blood flow in both hemispheres. The latter may be reflected in the ubiquitous decrease in global theta and alpha power.

**References**


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