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EDITORIAL

A continuing success story

In 2004 the WFSBP celebrated 30 years of fruitful existence. This year the WFSBP is proud to be celebrating the fifth birthday of its main publication, *The World Journal of Biological Psychiatry*. All those who have been involved in the production of *The World Journal of Biological Psychiatry*, and especially the Editorial Board, authors and reviewers, have assisted in the achievement of several milestones over the past five years, including acceptance for indexing by both the National Library of Medicine (Medline) and Thomson ISI. Among the various exceptional publications in past issues the internationally accepted WFSBP treatment guidelines represent one of the highlights. A special thanks also goes to the company Janssen Cilag for their financial support during the first four years, and to Lundbeck, who have committed themselves to supporting the Journal with an educational grant. We are now extremely pleased to announce that *The World Journal of Biological Psychiatry's* next era has begun in partnership with Taylor & Francis, a leading international academic publisher.

Taylor & Francis was first founded in 1798 when Richard Taylor launched the 'Philosophical Magazine', one of the first scientific journals to be produced by an independent company. It was the start of many close collaborations with scholarly societies. In 1852, Dr. William Francis, a chemist, joined Richard Taylor and continued the tradition of close links between the academic community and the company. With offices in several countries including Norway, Sweden, the UK, the USA, Singapore and Sydney, the Taylor & Francis Group publishes more than 1000 journals and around 2,800 new books each year, including a substantial list of medical titles. We are confident that such a renowned establishment will mean another great leap forward in the development of our Journal.

The collaboration with Taylor & Francis will bring a lot of improvements and increased professionalism for the Journal, whereby many of its well-known features will continue. The cover will remain unchanged. Registered WFSBP members will still receive the Journal as one of the important members' benefits (all members of national societies of biological psychiatry can become registered members

of the WFSBP). The scientific content of the Journal will continue to be the sole responsibility of the Editors, without any influence by the publisher or sponsors. However, we look forward to many positive, new features, including the following:

- Each issue will be bound with a spine detailing the volume and issue number, to facilitate identification.
- Within the next year, an internet-based system for manuscript submission and review will be introduced, which will help to speed up the whole process from submission to acceptance.
- The Journal will be available free-of-charge to registered WFSBP members and Journal subscribers in a member-only area on the WFSBP website. Non-members/-subscribers will have access to the abstracts of all papers and the tables of contents. Non-members will be able to purchase articles, which will help to increase revenue for the Journal. In keeping with the philosophy of the WFSBP, the Journal will be included in HINARI, a WHO programme that provides free or very inexpensive access to 2500 of the best medical journals to the world's poorest countries.
- Two years after publication, each issue will be made freely available on the WFSBP website public area.
- A search function will be introduced on the Journal website, allowing searches to be performed for individual authors or topics.
- A link will be set up from Pubmed to the Journal, meaning that papers in *The World Journal of Biological Psychiatry* found as a result of literature searches can be obtained by authors quickly and easily, which should ultimately have a positive effect on the impact factor.

This is one more exciting time for *The World Journal of Biological Psychiatry*. An impact factor for the Journal will be available in 2006, making it more attractive for some special publications and for colleagues interested in academic careers. We would therefore like to encourage you to continue to consider *The World Journal of Biological Psychiatry* when contemplating where to publish your work.

We also ask you to convey our enthusiasm to colleagues and members of your research group and to extend to them our invitation to publish the results of their investigations in *The World Journal of Biological Psychiatry*.

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REVIEW

Transcranial magnetic stimulation as a therapeutic tool in psychiatry

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Abstract

Transcranial magnetic stimulation (TMS) is a patient-friendly stimulation technique of the brain with interesting perspectives. In clinical psychiatry, limited data are available on activity in psychosis and anxiety, but much research has been done in depression. Major concerns on published papers are the inconsistency of used parameter settings, the restraint numbers of patients in randomised trials, the lack of real sham controlled studies and the quasi inexistent reproducibility of results. The most stringent meta-analysis of TMS in affective disorders found a modest, statistically significant antidepressant effect after 2 weeks of daily treatment of high frequency repetitive left dorsolateral prefrontal cortex stimulation. Although most results are rather weak and not convincing enough to promote TMS as evidence-based antidepressive therapy, they show a measurable action that should not be ignored. Preclinical and clinical effects were observed analysing heterogeneous data, and results comparing TMS to electroconvulsive therapy (ECT) in affective disorders are encouraging. Efforts should continue with emphasis on increasing homogeneity and reproducibility in data. Further refinement of stimulation parameters should be established, so that new and large double-blind, long-term, sham-controlled trials can bring us to better understanding and standardising TMS procedure, finally leading to definitive conclusions about its efficacy in psychiatry.

Key words: *Transcranial magnetic stimulation, biological psychiatry, depressive disorder*

Introduction

In TMS, a machine with a large condenser is used, connected to an electric isolated spool. The electrostatic energy in the capacitor is discharged and transformed into magnetic energy in the spool those functions as stimulation electrode. When fast oscillating magnetic fields are applied, electrical energy is transported through the brain, resulting in changes in neuronal activity. This current ($12\text{--}20\ \mu\text{A}/\text{cm}^2$) is of the same size-order as the one used in conventional electric brain stimulations (Epstein 1990; Sackeim 1994; Nobler et al. 2000; Wagner et al. 2004). Compared with the latter, during TMS no energy is lost in resistance of haired skin, soft tissues and the skull. Less stimulation energy is needed, resulting in less pain. Furthermore, only the brain region within reach of the magnetic field activity (1.5–2 cm from the surface of the induction spool) is directly affected. Generalised motor activation and seizures, normally needing anaesthesia, therefore can be avoided (George et al. 1999).

Barker et al. at the University of Sheffield developed the first compact magnetic stimulator in 1985. In the same year, Merton in London carried out the first sessions of transcranial motor cortical magnetic stimulation (Barker et al. 1985; Pascual-Leone et al. 1997; George and Belmaker 2000). Initially 'single-pulse' stimulators were used, with a limited range of stimulation capacity. Current stimulators can produce very high intensities and multiple impulses in a high tempo (trains) with a short interval, resulting in repetitive TMS (rTMS) (Pascual-Leone et al. 1997; George and Belmaker 2000).

TMS was at the beginning a neurological research tool and used in the exploration of motor functions and brain mapping. Later, single pulse and rTMS proved to be useful in diagnostics and therapy (spinal and cranial neurosurgery, revalidation of central and peripheral motor dysfunctions, exploration hemispherical dominance).

In psychiatry rTMS is used for the study of higher cortical functions (cognition, emotion, behaviour) and in the therapy of major clinical syndromes, such

as psychosis, anxiety and principally affective disorders. The first antidepressant TMS study dates from more than a decade ago (Hoflich et al. 1993). Although early studies showed encouraging results, a strong and consistent evidence of antidepressive activity has not been proven. In the past years, several meta-analyses have been published. Some countries in the world have recognised TMS as an official antidepressive therapy (e.g., Canada and Israel), others, like the USA, are waiting for further evidence.

This article will discuss the TMS procedure and its possible underlying working mechanisms. It overviews the literature concerning its therapeutic potentials in psychiatry as well as safety and procedural refinement matters.

Standard procedure TMS in psychiatry

During a session of TMS the subject, awake and alert, is placed in a chair in most cases. The subject receives two earplugs to minimise the impact of the disturbing 'clicking' noise during the stimulation. The stimulation coil, in most recent studies figure-eight shaped, is placed over the skull. The stimulation site and the amount of needed stimulation energy are determined at the beginning of each session (Ziemann and Hallet 2000). For most psychiatric trials, this is done by determining the individual motor threshold (MT) for the abductor pollicis brevis (APB) muscle of the right thumb. The motor threshold is the lowest magnetic intensity necessary for one TMS pulse to provoke an electromyographic detectable motor evoked potential (MEP) of a defined minimal size (e.g., 50 μ V) in this muscle in 50% of at least five measurements (George et al. 1998; Pascual-Leone et al. 2002). From the optimal position for stimulating APB, the coil is shifted carefully, keeping angulation, tilting and direction, to a predefined standardised stimulation site. In depression the target place to stimulate is the dorsolateral prefrontal cortex (DLPF), situated about 5 cm forward (rostral) and on a parallel to the midline (Grunhaus et al. 2000; Janicak et al. 2002; Grunhaus et al. 2003). The intensity of the stimuli that will be applied is fixed at a certain percentage of the energy that was needed to achieve MT.

In some diagnostic and many of the research conditions single pulse TMS is applied, but in most clinical trials each session consists of sequential trains of repetitive magnetic field pulses at a certain frequency (1–20 Hz). Each train lasts several seconds and between two of them there is a constant intertrain interval of some seconds as well. A variety of treatment durations and numbers of sessions have

been studied, but the majority of clinical studies applied a treatment schedule of one session a day, 5 days a week, for one or more following weeks.

How TMS influences neuronal functioning

TMS creates fast oscillating magnetic fields. Changing magnetic fields affecting the cortex over a short time period can induce depolarisation (George et al. 1996a). The magnetic fields caused by TMS are situated perpendicular on the brain surface. The cortical interneurons, in an orthogonal position to the magnetic field, are probably more influenced than the cortical brain cells themselves. The oscillation speed in the induction spool and in the induced currents plays an important role in the efficacy of the TMS technique. To depolarise neurons, the current in the induction spool should start, stop, and reverse within $\pm 300 \mu$ s (Barker et al. 2002). This means that a stimulation frequency higher than 1 Hz is needed to achieve neuronal activation. Lower frequencies have showed to suppress neuronal activity. Currently it is accepted that high frequency rTMS (>1 Hz) causes immediate neuronal excitation, whereas low frequency rTMS (≤ 1 Hz) causes immediate neuronal inhibition. Underlying possible mechanisms are still subject of preclinical research (Fitzgerald et al. 2002; George et al. 2002, 2003). Furthermore, it may be presumed that high frequency rTMS, enhancing neuronal excitability, can induce long-term potentialisation (LTP) intersynaptic transmission. Analogously low frequency rTMS would cause long-term depression (LTD). This hypothesis seems validated for motor cortex neurons in studies applying rTMS to a single neuron in cultures, by findings in rats and by some human in vivo studies as well (Chen et al. 1997a; Stanton and Sejnowsky 1989; Bear 1999; Malenka and Nicoll 1999; Wu et al. 2000; Iyer et al. 2003; Modugno et al. 2003; Ogiue-Ikeda et al. 2003). However, as numerous unpublished studies failed to reproduce these findings (George et al. 2002), the exact mechanism of modification of inhibitory and excitatory circuits remains uncertain. Research using paired pulse TMS may bring more clarity. In this method, a subthreshold stimulus precedes a supra-threshold stimulus. The response to this stimulation method may be increased (facilitation, probably glutaminergic) or decreased (inhibition, probably through two different GABA-ergic circuits) depending on the interstimulus interval (Fitzgerald et al. 2002; George et al. 2003).

Besides the oscillation speed, other factors determine the induced current: the current strength in the induction spool and the number of windings in the electrode (George et al. 1996a, 1998).

The shape of the created magnetic field determines which part of the brain under the spool is reached, within margins of 1.5–2 cm of the probe. The magnetic field shape itself is dependent on the shape of this stimulation electrode (George et al. 1996, 1998, 1999). Initially spools had a circular diameter (80–100 mm), the most efficient shape for stimulation motor cortex. The induced current in the brain is circular and parallel to the plane of the spool, but in reversed direction. The strongest current circuits are located just below the spool and they become exponentially weaker the more they are distant from the centre of the round spool. Over the past few years, new electrodes have been introduced. The so-called figure-eight-shaped electrode consists of two metal spiral wires placed next to each other. The maximum of induced current is created in the middle of the electrode, where the both wires converge. This electrode is especially useful for stimulation of more precise and smaller determined brain zones (as is the case of brain mapping and antidepressant TMS research).

TMS can only directly influence the neurons within reach of the magnetic field. Deeper situated neurons probably can become activated indirectly via cortical interconnections and redundant cortical–subcortical loops. Functional neuro-imaging studies, hormonal changes and changes in brain metabolism after TMS support this hypothesis (Alexander et al. 1986; George et al. 1996b; Bohning et al. 1999; Nobler et al. 2000; George et al. 2002, 2003).

Effect on higher cortical circuits and functions

TMS induces generalised depolarisation in the brain regions within its reach (George et al. 1996a). Depolarisation in the motor cortex results in a movement. Depolarisation in other cortical regions should result in excitation or inhibition (dependent on the frequency), reflected in changes in higher cortical functions (e.g., depolarisation of the prefrontal cortex should result in change in behaviour or mood).

Effects on memory and cognition

Much of the data concerning cognition comes from clinical antidepressant rTMS trials measuring cognitive side effects. These will be discussed later. Earlier cognition studies mainly focused on short-term interference of TMS with memory and recall domains, language and speech-related functions and visual tasks. There were both transient disruption and enhancement of functioning, dependent on the stimulation parameters (Fitzgerald 2002). Preclinical

studies using paired pulse stimulation are valuable in unravelling the exact mechanisms behind those observations (Robertson et al. 2003; Calvo-Merino and Haggard 2004). Recently, improvements on the digit symbol substitution test and verbal fluency have been observed after stimulation in healthy volunteers, as well as improvements in cognitive flexibility and conceptual tracking in depressed patients (Jenkins et al. 2002; Moser et al. 2002).

Effects on reality testing

Diverse pathophysiological theories explain symptoms of psychosis. Hypo- or hyperfunctioning in different brain areas are thought to result in a dysfunction of especially the fronto-subcortical loops and their connections with deeper grey nuclei. Current TMS devices cannot produce a magnetic penetration power to reach these brain areas directly. Chances of influencing a psychotic process as a whole with TMS thus are small (Klein et al. 1999; McNamara et al. 2001).

Effects on mood regulation

Most mood researchers believe in the concept of a complex mood regulating system, consisting out of several parallel networks including the prefrontal cortex, the limbic structures and the striatum. Among these, the prefrontal cortex is the only region in reach of rTMS. TMS aimed at the prefrontal cortex therefore can be expected to influence mood (George 1994; George et al. 1994a,b, 1995a,b, 1996a, 1997a, 1998; Ketter et al. 1996; Mayberg et al. 1999; Kimbrell et al. 2002; Schlaepfer et al. 2003).

Animal TMS studies provide support to this hypothesis. Rodent rTMS studies have reported antidepressant-like behavioural and neurochemical effects, such as enhancement of apomorphine-induced stereotypy and reduction of immobility in the Porsolt swim test (Fleischmann et al. 1996; Tsutsumi et al. 2002). Enhanced forebrain serotonin output and modulation of the extracellular serotonin and its receptor functions have been observed following rTMS administration in rats (Ben-Sachar et al. 1999; Juckel et al. 1999; Kole et al. 1999; Kanno et al. 2004a). Extra cellular levels of dopamine and glutamate in the nucleus accumbens – a major region implicated in reward circuitry and depressive disorders – were increased after acute TMS over rat and monkey frontal cortex (Zangen and Hyodo 2002; Kanno et al. 2004b; Ohnishi et al. 2004). Repetitive TMS has also induced electroconvulsive shock-like biochemical and genetic

changes in animals: there were similar changes in brain monoamine neurotransmission and enhancements of c-fos in parietal cortex and hippocampus (Hausmann et al. 2001; Pridmore et al. 2001; George et al. 2002). However, these findings were not always reproducible and often confounded by methodological problems (Lisanby and Belmaker 2000). Most of the studies applied stimulation of the whole brain of small animals, which makes it difficult to extrapolate findings to what is happening during human focal TMS (Weissman et al. 1992; Padberg and Möller 2003).

Nevertheless, some imaging studies in humans reported findings similar to those in animals and in accordance to most accepted mood regulation hypotheses. For example, dopamine release in the ipsilateral caudate nucleus after left-sided prefrontal TMS has been observed (Strafella et al. 2001, 2003). This observation can be linked to the recent finding that the facilitation of mesolimbic or nigrostriatal dopamine neurotransmission could be the mechanism of action behind treatment efficacy in treatment refractory depressed patients (Inoue 2003).

Also human neuro-endocrine research adds support to the possibility of TMS influencing mood. In depressed patients, a disinhibition of the limbic–hypothalamic–pituitary–adrenocortical (LHPA) axis is well documented. Normalisation of its function has been associated with clinical response to classical antidepressant therapy. Similar changes were measured in studies applying rTMS (George et al. 1996b; Cohrs et al. 1998; Pridmore 1999; Reid and Pridmore 1999; Szuba et al. 2000, 2001; Pridmore et al. 2001; Burt et al. 2002; Padberg et al. 2002a; Padberg and Möller 2003; Zwanzger et al. 2003).

Next to these preclinical studies, a few studies investigated the clinical effect of prefrontal rTMS on mood in normal volunteers (Schlaepfer et al. 2003). Some show transient brief and discrete mood-lifting or -lowering changes with stimulation of the left dorsolateral prefrontal cortex (left DLPF) or right dorsolateral prefrontal cortex (right DLPF) (George et al. 1996b; Pascual-Leone et al. 1996; Dearing et al. 1997). This raises an important mood issue relevant to TMS: laterality of the brain. According to the laterality hypothesis of mood, the left hemisphere would be responsible for positive emotions while the right hemisphere would evoke negative emotions (Padberg and Möller 2003). This could explain why dysfunctions in the left orbitofrontal and prefrontal cortex were noted in depressed patients, ischemic lesions in the left prefrontal cortex also resulted more often in post-stroke depression than right-sided lesions and anatomical and functional

imaging (CAT, MR, SPECT and PET) studies in primary and secondary depressions show abnormalities in the left prefrontal cortex. Some TMS studies in healthy subjects also support this laterality hypothesis. One study using low frequency rTMS at 130% MT in female subjects showed right-sided stimulation to result in selective attention towards angry faces in a pictorial emotional stroop task, whereas left-sided identical stimulation produced selective attention away from them (d'Alfonso et al. 2000). In other studies mood states varied from reported feelings of frustration, sadness and even spontaneous weeping after right DLPF TMS to feelings of happiness after left DLPF TMS. There were some cases of short-lasting hypomania after left DLPF rTMS in healthy human volunteers (Nedjat and Folkerts 1999). Recent studies, however, failed to replicate lateralised effects of prefrontal rTMS on mood (Mosimann et al. 2000; Padberg and Möller 2003). For example, lower frequencies (1 Hz), supposed to suppress brain excitability, applied to the right DLPF did not induce mood changes in 19 healthy volunteers (Jenkins et al. 2002). Differences in used TMS parameter settings can partly explain these incongruous results.

Based on much of these data, one of the pioneers in the psychiatric TMS research field, M. George, postulated the theory that chronic, frequent, subconvulsive TMS of the prefrontal cortex over several weeks may initiate a therapeutic cascade of events both in the prefrontal cortex and in connected limbic regions, thereby alleviating depression. Not only clinical trials but also recent imaging studies confirm this hypothesis (George et al. 2002). Devices are being developed that allow direct functional imaging (fMRI, PET) of TMS effects (Bohning et al. 2003; George et al. 2003; Neggers et al. 2004). Serial scans in depressed patients undergoing high frequency rTMS (at 20 Hz) over the left prefrontal cortex showed increased activity in the rostral anterior cingulate and other limbic regions. Low frequency left prefrontal rTMS (at 1 Hz) seemed to produce more circumscribed decreases in brain activity (Teneback et al. 1999; Paus et al. 2001; Strafella et al. 2001; Mitchel 2002; Shajahan et al. 2002). In another study with healthy volunteers, where reduction in self-reported positive affect and vitality were noted after 10-Hz rTMS over the left mid-dorsolateral frontal cortex (MDLFC), changes in blood flow were seen in left MDLFC and in a number of affect-relevant brain regions, including the perigenual anterior cingulate gyrus, insula, thalamus, parahippocampal gyrus, and caudate nucleus (Barrett et al. 2004). Clinical studies registering self-rated mood assessments showed discrete daily progressions consistent with functional imaging data

showing repeated subtle changes in mood-regulating circuits, suggesting that during each treatment session, the mood-regulating circuit is being activated and slightly normalised. The predictive values of these subtle changes remain unclear, but they can help to refine stimulation parameters more accurately (Szuba et al. 1999; Nahas et al. 2003).

Functional imaging studies also bring up new elements to refine the above-stated hypothesis. For example, prefrontal TMS at 80% MT produces much less local and remote blood flow changes than does 120% MT TMS, suggesting the need of a suprathreshold stimulus (Nahas et al. 2001a). Another important issue was revealed with PET scans, [¹⁸F]fluorodeoxyglucosis and HMPAO SPECT scans: baseline brain activity state is an outcome factor for high frequency rTMS treatment in depression. This means that a subgroup of depressive patients with global or focal basal hypometabolism would be more susceptible for successful treatment than others (Nadeau et al. 2002). Again these statements need to be interpreted with caution, as one SPECT study found different correlations between recovery from depression and perfusion rates in different brain regions (negative in limbic structures, positive in several neocortical areas) (Mottaghy et al. 2002).

Clinical applications in psychiatry

Most clinical psychiatric TMS research has been focusing on the hypothesised antidepressant efficacy. Possible beneficial effects in other psychiatric disorders have been investigated less extensively in some recent studies.

Depression

The first (open) studies applied single-pulse TMS with a big open or circular stimulation electrode, placed on the vertex, stimulating often different brain areas, at frequencies less than 0.3 Hz (Schlaepfer et al. 2003). Later the technique changed and rTMS was mostly used. Since 1995, the figure-of-eight-shaped stimulation coil, introduced by George and co-workers, is more standard. It improves penetration and focality of the magnetic field compared to the circular coil (Pridmore et al. 2001).

Some of the initial (open) rTMS clinical trials found an antidepressant effect of high frequency rTMS (10–20 Hz) over the left dorsolateral prefrontal cortex (George et al. 1995a; Epstein et al. 1998; Figiel et al. 1998; Pridmore et al. 1998). Other studies used stimulation reversed parameters, namely at a low frequency (1 Hz) and over the right dorsolateral prefrontal cortex, with a circular open

stimulation coil. Both methods seemed safe and induced antidepressant activity (Feinsod et al. 1998). Later, a growing number of double-blind and sham-controlled studies confirmed those preliminary findings (Pascual-Leone et al. 1996; George et al. 1997b; Klein et al. 1999; Tormos et al. 1999; Schlaepfer et al. 2003), adding support to the above-discussed laterality hypothesis in mood regulation. High frequency rTMS over the left DLPF (left prefrontal rTMS) could be effective via activation, low frequency stimulation over the right DLPF (right prefrontal rTMS) via local inhibition of the underlying cortical circuits (Pascual-Leone et al. 1994; Chen et al. 1997a; Speer et al. 2000; Fitzgerald et al. 2002).

Meta-analyses. All studies between the late 1990s and 2002 achieving a certain minimum of methodological quality (selection made of maximum 15 trials) were included in five independent meta-analyses (Holtzheimer et al. 2001; McNamara et al. 2001; Burt et al. 2002; Kozel and George 2002; Martin et al. 2003a,c). The overall conclusion seems to point out an antidepressant efficacy by daily stimulation over the left DLPF cortex with middle-high stimulation frequency (≤ 20 Hz) at intensities just above or below MT. Reported effects take several weeks to build up and are temporarily, but significantly greater than those achieved with sham stimulation (Loo et al. 1999). Not much data are available concerning follow-up: only information concerning five patients has been reported (Holtzheimer et al. 2001; McNamara et al. 2001).

Looking more into detail, a discrepancy exists between results and conclusions of different meta-analyses. Some characteristics of most clinical trials included in the meta-analyses can be found in Table I. As shown, study material differs substantially with respect to sample size, patient description, stimulation parameters and study design, complicating adequate comparison and evaluation (Holtzheimer et al. 2001; Martin et al. 2003c; Padberg and Möller 2003). The Cochrane analysers are especially cautious (Martin et al. 2003a). They rigorously chose to separate analyses of the four main rTMS conditions (combinations of high or low frequency, with right or left prefrontal stimulation), considering them each as total different treatment modalities. This results in a strong reduction of total numbers of included patients for each condition, limiting possibilities to demonstrate significant differences between sham and active rTMS (Padberg and Möller 2003).

The small sample sizes (between six and 70 patients for the Cochrane meta-analysis) make it impossible to define the subgroups of patients who would benefit best from this treatment (McNamara

Table I. Included studies in the Cochrane analysis (Martin et al. 2003a,c; Kozel and George 2002).

	George et al. 1997b	Kimrell et al. 1999	Loo et al. 1999	Padberg et al. 1999	Avery et al. 1999	Klein et al. 1999	Berman et al. 2000	Eschweiler et al. 2000	Garcia-Toro et al. 2001a	Garcia-Toro et al. 2001b	George et al. 2000a	Manes et al. 2001	Szuba et al. 2001
Study design	Crossover	Crossover	Parallel	Parallel	Parallel	Parallel	Parallel	Crossover	Parallel	Parallel	Parallel	Parallel	Parallel
Number of patients	12	13	18	18	6	70	20	10	35	22	30	20	14
Medication resistant	No	NA	Yes	Yes	Yes	No	Yes	NA	Yes	No	Yes	Yes	No
Medication free	9/12 patients	9/13 patients	No	1/6 patients	No	No	Yes	No	Yes	No	Yes	Yes	Yes
DLPF cortex laterality	Left	Left	Left	Left	Left	Right	Left	Left	Left	Left	Left	Left	Left
Sham coil orientation	45°	45°	45°	90°	45°	90°	45°	90°	90°	90°	45°	NA	NA
Intensity (% MT)	80	80	110	90	80	110	80	90	90	90	100	80	100
Stimulation frequency (Hertz)	20	1	10	0.3	10	1	20	10	20	20	20	20	10
Number of daily pulses	800	800	1500	250	1000	120	800	2000	1200	1200	1600	800	1000
Train duration	2	2	5	NA	5	60	2	10	2	2	16000	2	5
Trains per session	20	20	30	NA	20	2	20	20	30	30	40	20	20
Number of sessions	10	10	20	5	10	10	10	10	10	10	10	5	10
rTMS response (HDRS reduction > 50%)	1/12	0/13	0/9	0/6	1/4	17/35	1/10	NA	5/17	4/11	3/10	3/10	NA
SHAM response (HDRS reduction > 50%)	0/12	0/3	0/9	0/6	0/2	8/32	0/10	NA	1/18	3/11	0/10	3/10	NA
Mean decrease HDRS Raw: in rTMS	4.17	-1.15	4.89	1.7	10.5	12.1	14	5.2	7.05	11.6	7.8	NA	NA
Raw: in SHAM	-3.38	0.33	4.78	-1.30	4.50	5.60	0.20	-1.90	1.77	12.1	12.8	NA	NA
%: in rTMS	14%	-4%	23%	6%	49%	47%	38%	23%	26%	45.2%	26%	NA	NA
%: in SHAM	-16%	1%	19%	-6%	23%	22%	1%	-9%	7%	45.2%	49%	NA	NA
Effect size Hedges	1.37	0.32	-0.18	0.44	0.60	0.74	1.05	0.21	1.07	0.14	0.65	0.30	NA
Variance	0.34	0.20	0.22	0.25	0.88	0.25	0.20	0.34	0.11	0.18	0.15	0.20	NA

DLPF, dorsolateral prefrontal; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale.

et al. 2001). In most studies, patients continued taking antidepressant treatment. Repetitive TMS was in these cases may be only an augmentation strategy (Burt et al. 2002). Therapy-resistant patients were selected, except in one trial where less severely depressed patients were studied. The results of this one study were the most promising of all included trials: a response rate of 49% (Klein et al. 1999). This suggests that less severely depressed patients may benefit more from this treatment than others. There was, however, a large response rate in the sham population as well, raising some doubts about methodological biases in this trial (Holtzheimer et al. 2001).

One of the methodological difficulties complicating adequate interpretation of trials concerns the placebo or sham condition (Janicak et al. 2002). The creation of an ideal sham coil poses a problem: how can a device induce the same visual and subjective sensory experiences at the stimulation site and produce similar acoustic artefact, time locked to the scalp sensation, in absence of this magnetic field? Because of the lack of such an electrode design, most clinical research found a solution in altering the orientation sense of the same coil used in active treatment condition. In most cases, the figure-eight-shaped electrode is held at an inclination of 45 or 90° towards the skull. Loo et al. (1999), however, found that such sham stimulation could induce a firm antidepressant result. In another study, the same authors examined seven different “sham” figure-eight coil positions in nine healthy subjects. None of these positions met the criteria for an ideal sham, because coil inclinations associated with a better scalp sensation were also more likely to measurably stimulate the cortex (Loo et al. 2000). Concluding, it can be stated that the 45 or 90° inclination probably offers the best trade-off between effective blinding and truly inactive stimulation (Loo et al. 2000; McNamara et al. 2001, Fitzgerald et al. 2002). The use of a “real” sham coil offers the only solution to the above-discussed problem. Investigations to develop such a coil are in progress (McNamara et al. 2001).

Another remark concerns the problem of adequate blinding in treatment designs. When sham and treatment design are not completely similar, the professional in charge of applying the technique must know whether a patient belongs to the treatment or control group. The interaction of the patients with the researchers in such a single-blinded condition could provide different levels of motivation to both participants (Martin et al. 2003a).

The choice of depression evaluation scales can also influence the results. Most studies used a version of the Hamilton Depression Rating Scale

(HDRS) and/or the Beck Depression Inventory (BDI) scores. The Cochrane reviewers pointed out that the comparison of data through different scales could affect internal validity. They advise including additional, more objective outcome measures: hospital discharges, treatment-free period, readmission rates, period of inability to work (Martin et al. 2003a,c).

Recent trials. Since the publication of the latest meta-analysis, new trials have been published. One study, using the currently most successful stimulation design, failed to replicate significant antidepressant effect, but noted for patients with a better response a shorter duration of the current depressive episode (Holtzheimer et al. 2004). Some authors tried lower (subthreshold) stimulation intensity to achieve antidepressant efficacy. Boutros et al. (2002) found no significant difference applying high frequency rTMS (20 Hz) at 80% MT. Padberg et al. (2002b) compared 90%MT to 100%MT in high frequency rTMS (10 Hz) and found less antidepressant effect with the lower intensity. These findings support the statement that the antidepressant effect of rTMS significantly increases with stimulation intensity (Padberg et al. 2002b).

The homogeneity in efficacy of the high frequency stimulation range was also subject to additional research. Comparison of 5, 10 and 20 Hz rTMS showed no differences in HDRS reductions in one study, but the stimulation intensity used was low (80% MT) (Shajahan et al. 2002). Another trial using 5 Hz left prefrontal rTMS at 110% MT in 23 bipolar patients did not show therapeutic differences compared to sham (Nahas et al. 2003).

Other recent trials focused on the laterality hypothesis using high frequency left prefrontal rTMS as well as low frequency right prefrontal rTMS. Most researchers found indeed a similar significant antidepressant effect compared to sham, lacking any differences between the two described conditions (Conca et al. 2002; Hoppner et al. 2003; Kauffmann et al. 2004). One author tried to apply bilateral prefrontal rTMS, failing to show differences in mood improvements after 3 weeks (Loo et al. 2003a). The importance of laterality and stimulation frequency and especially the correct combination of both factors seems to be crucial. The underlying working mechanisms are still unknown.

Fitzgerald et al. (2003) focused on total amount of administered pulses and total duration of treatment. They hypothesised that response would increase with a longer period of stimulation, due to an accumulated dose (number of pulses) or to longer treatment duration. They carried out a 4-week double-blind, randomised, sham-controlled trial

with 60 patients. There was only a significant antidepressant effect after 4 weeks but both in low and high frequency rTMS, with a similar magnitude, despite the fact that low frequency rTMS consisted of considerably fewer pulses per session. If the number of accumulated pulses is pivotal, it can be hypothesised that 1-Hz stimulation with an equal number of pulses as in the high frequency rTMS condition, would have produced better results. Due to this and taking into account safety and tolerability, low frequency rTMS may prove to be a first-line rTMS strategy in depression. Crossover to high frequency rTMS in non-responders could be the following step in treatment strategy (Fitzgerald et al. 2003).

How to optimise rTMS antidepressant properties. Antidepressant effects of rTMS in trials depend among others on patient characteristics, study designs and stimulation parameters (Table II). Concerning patient characteristics, no large or systematically replicated data is available, but it seems that younger patients, not therapy-resistant and not psychotic, without prefrontal cortical atrophy but with somatic signs of anxiety would benefit best from rTMS (Padberg and Möller 2003). Some consensus has emerged regarding therapeutic settings but the ideal parameter combination is still open to debate.

The shape and size of the stimulation electrode is one of the important topics. The currently most used figure-of-eight coil has the advantage to produce a cone-shaped volume of concentrated magnetic field, narrowing and increasing in strength towards the apex. It cannot, however, create a remote isolated spot with high intensity surrounded by areas of lower intensity. This would be interesting because deeper situated brain regions (e.g., the limbic system) could then be targeted, without affecting surrounding areas responsible for undesired side effects (Bohning 2000). To achieve this, the diameter of coils should be reduced. However, the smaller the coil, the greater the stimulation intensity required to produce similar depth of penetration (Fitzgerald et al. 2002).

Moreover, heating (and the risk of scalp burns) is augmented with decrease of electrode diameter (Jalinous 2002; Ruohonen and Ilmoniemi 2002).

The stimulation point is a parameter that determines if prefrontal cortex is efficiently stimulated. In most studies, the left hemisphere was stimulated, and a rule-based algorithm, which was discussed previously, was used to find the prefrontal cortex. This standardised method ignores anatomical brain differences and head sizes (George et al. 2002; Grunhaus et al. 2003). In one imaging study, only seven out of the 22 subjects had the coil placed exactly above the intended brain area. It appeared that the measure at 5 cm rostral to the MT point could be too short to target this area (Herwig et al. 2001a). It remains an unanswered question if these subtle differences are responsible for significant differences in therapeutic effects. A better coil site localisation would be possible with MRI guidance (Grunhaus et al. 2003; Neggers et al. 2004). Several groups (Herwig et al. 2001b; Neggers et al. 2004) have developed such a neuro-navigational approach. Recently, a first clinical double-blind, randomised trial using this stereotactic coil-navigation was published (Herwig et al. 2003).

Another essential parameter is the stimulation intensity. It is based on the individual motor threshold, as discussed above. Looking at the existing data, an intensity of at least 80% MT and higher intensities (90–110% MT) may produce the most robust effects. Using the same stimulation power to activate prefrontal neurons as needed for motor neuron cells in the motor cortex (MT) can result in inappropriate dosing (Dolberg et al. 2002). It ignores the fact that higher intensities are perhaps needed to reach the prefrontal cortex than the motor cortex. This is especially of concern in elderly patients (with prefrontal atrophy), in whom coil–cortex distance increases (Kozel et al. 2000; McConnell et al. 2001; Mosimann et al. 2002; Padberg et al. 2002b; Grunhaus et al. 2003). Some authors, however, found that there may be an association between the excitability of the prefrontal and motor cortex,

Table II. Parameters (patient, study design and stimulation design related) which can affect results of TMS.

Patient characteristics	Stimulation parameters	Study design factors
Treatment-resistance	Machine/coil type	Sham parameters (45/90°)
Age	Location of stimulation site	Blindedness
Concurrent medication	Intensity	Crossover versus parallel-groups
Type and severity of depression	Total number of TMS pulses:	Randomisation procedures
Right/left handedness	Frequency of stimulation (20, 5, 1 Hz)	
Onset/duration current episode	Train duration	
Scalp-cortical distance	Number of trains	
In- or out patient	Number of sessions (duration)	
Psychotic symptoms	Intertrain interval	
	Intersession interval	

suggesting that MT determination could be preserved (Kahkonen et al. 2004). An alternative to the motor measure is to calculate the dose based on a formula which takes into account the individual distance from scalp to prefrontal cortex (measured with MRI) and the exponential drop in magnetic field strength with increasing distance from the coil (Bohning et al. 2000; Kozel et al. 2000; Nobler et al. 2000; McConnell et al. 2001).

The influence of different stimulation frequencies (1–20 Hz) is closely related to laterality in brain mood systems, as discussed above. Most trials point to the direction of an antidepressant effect from left prefrontal high frequency and from right prefrontal low frequency rTMS, but some contrasting observations have also been found (Holtzheimer et al. 2001; Burt et al. 2002). Functional imaging, such as SPECT, can help to discover the underlying mechanisms of different stimulation frequencies and laterality (Loo et al. 2003b).

Variable amounts of rTMS pulses per session have been administered in clinical trials. The most beneficial effects were found with 1200–1600 stimuli a day (George et al. 1997b; Fitzgerald et al. 2002). The total number of pulses depends on frequencies, train durations and number of trains (Table I).

The intertrain interval is an important safety factor. Seizures have been reported with intervals below a certain duration. It has been suggested that at 20 Hz stimulation at 100% MT, intertrain interval duration should last at minimum 5 s and certainly not become lower than 1.2 s (Chen et al. 1997b; Fitzgerald et al. 2002). If intensity exceeds 110% of MT or frequencies 20–25 Hz, it is advised to respect a minimum of 60 s. A general rule proposed by George et al. suggests an intertrain interval as long as the stimulation period (Chen et al. 1997b; Fitzgerald et al. 2002; George et al. 2002; Pasucal-Leone et al. 2002).

Finally, duration of treatment and session frequency are also important influencing factors. Emerging data suggests that therapeutic effects of rTMS take several weeks to build up, whereas most published studies only studied effects concerning 1 or 2 weeks (George et al. 2002). Regular treatment regimens consisted of five sessions a week, one session daily, mostly during two following weeks (Pridmore et al. 2001). Obviously, the matter of maintenance therapy remains unsolved as well. Schule et al. (2003) followed some patients taking antidepressant medication as maintenance therapy following rTMS. Their results suggested that antidepressant pharmacotherapy is able to further improve the clinical response to rTMS and that responders to rTMS monotherapy should receive

subsequent psychopharmacological treatment without interruption in order to avoid a deterioration of symptoms. The sparse data of seven patients who underwent magnetic stimulation maintenance therapy (1 session per week) for about 25 weeks showed three patients without relapse after 1 year (George et al. 2002).

Comparing rTMS to ECT. Basic research showed that rTMS and ECT produce some similar biochemical and neurophysiological changes (Pridmore et al. 2001; Hausmann et al. 2001; George et al. 2002; Bolwig 2003). Recent work focused on clinical results in ECT versus rTMS treatment groups (Table III). Five clinical trials and one study combining one ECT session with four TMS session a week have been published. One other study presented follow-up data (Grunhaus et al. 2000; Pridmore et al. 2000a,b; Dannon et al. 2002; Grunhaus et al. 2003; O'Connor et al. 2003). The results in these trials showed positive results of similar depth in both groups. Considering the patient compliance and safety profile of rTMS, the question raises if rTMS, alone or in combination with ECT, could not replace or reduce the number of ECT sessions (Grunhaus et al. 2000; Burt et al. 2002; Janicak et al. 2002; O'Connor et al. 2003). However, some methodological concerns still exist. The criticisms concern a lack of adequate blinding and sham control groups, the concomitant pharmacological treatments, the length of treatment period, sample sizes, the selection of mainly ECT-referred depressed patients. Furthermore, in severely and psychotic depressed patients, ECT showed superior results. A possible explanation is that rTMS has a sub convulsive effect and that it can only affect a relatively small focal cortical region, while the antidepressant effect of ECT is related to its generalised electrical and clinical convulsive effect (Fink et al. 1999). A more powerful hippocampal expression of immediate-early genes in animals after ECT, resulting in a greater formation of new cells in this region could be linked to this convulsive effect (Bolwig 2003).

Based on those findings and the fact that there was higher hippocampal long-term potentiation with more powerful transcranial magnetic stimulation in rats (Ogiue-Ikeda et al. 2003) at frequencies and intensities that evoke seizures under anaesthesia, it seems a reasonable option to do the same in humans to achieve firm antidepressant effects. This method is called magnetic seizure therapy (MST). Theoretically, the induced electric field of unilateral MST remains more focal and limited than that induced by ECT. This offers the advantage to target mood-regulating areas more precisely, avoiding elec-

Table III. Trials comparing ECT versus. rTMS directly in the treatment of depression.

	Grunhaus et al. 2000	Pridmore et al. 2000b	Janicak et al. 2002	O'Connor et al. 2003	Grunhaus et al. 2003
Number of patients	40	32	25	28	40
Study duration	4 weeks	4 weeks	4 weeks	2-4 weeks	4 weeks
Coil type	Figure-eight				Figure-eight
TMS					
TMS site	Left DLPFC	Left DLPFC	Left DLPFC	Left DLPFC	Left DLPFC
Intensity (%MT)	90% MT	100% MT	110% MT	90% MT	90% MT
Frequency (Hz)	10 Hz	20 Hz	10 Hz	10 Hz	10 Hz
Train duration	2 s 6 s	2 s	5 s		6 s
Intertrain interval		28 s	20-50 s		30 s
Trains per session	20	30-35	20		20
Stimuli per session	400 1200	1200	1000	1600	1200
ECT					
ECT site	Unilateral Uni → bilateral	Unilat non-dominant hemisphere	Bitemporal	Unilateral	Unilateral (n = 13) Bilateral (n = 7)
Charge (mC)	2.5 × threshold	504 mC			481.6/382 mC
Aimed seizure duration					31-33 s
EEG Δ duration	>25 s		48.93 s		50-60 s
Comparison TMS-ECT					
Number of patients	8 12	16	13	14	20
Medication free	Yes	No	Yes	NA	Yes
Treatment regime (number of sessions)	5/wk (to 20)	5/wk (12.2)	5/wk (to 20)	5/wk (to 10)	5/wk (to 20)
HDRS remission response (%)		68.8%	46%	<ECT	55%
HDRS% improvement	40.3%	55.6%	55%	<ECT	45.5%
BDI% improvement	NA	45.5%	NA	NA	NA
ECT	12 8	16	9	14	20
ECT	No	No	Yes	NA	Yes
ECT	9.6	3/wk (6.2)	3/wk (4-12)	3/wk (6-12)	NA (10.3)
ECT		68.8%	56%	>TMS	60%
ECT	60.6%	66.4%	56%	>TMS	48.2%
ECT	NA	69.1%	NA	NA	NA

DLPFC, dorsolateral prefrontal cortex; MT, motor threshold; wk, week; HDRS, Hamilton Depression Rating Scale; HDRS, remission response, % of patients achieving HDRS endpoint scores below 9 and/or >50% HDRS scores improvement. BDI, Beck Depression Inventory.

tric waves to spread to other regions. The medial temporal regions for example, essential in cognitive functioning, may be less affected (Lisanby 2002). Preliminary results from animal models based on studies with rhesus monkeys support the statement that MST could be a safer and tolerable alternative to ECT. Thirteen monkeys received MST, all having generalised tonic-clonic seizures resembling ECT-induced seizures following 2–5 s of magnetic stimulation at 40 Hz, 90–100% of maximal stimulator output. No adverse effects or neuropathological findings were observed (Lisanby et al. 2003).

Clinical data of 22 patients treated with a combination of ECT and MST have been discussed. Tolerance was excellent and the HDRS scores decreased significantly during MST sessions in at least two case reports. In a recent randomised, double-blind trial 10 patients had significantly fewer and less severe muscle aches, subjective memory complaints and headaches. MST was in this trial also associated with faster recovery of orientation, and was superior to ECT on measures of attention, retrograde amnesia, and category fluency (Lisanby et al. 2001; Burt et al. 2002; Lisanby et al. 2003; Kosel et al. 2003).

Bipolar disease, manic state

An anti-manic effect of rTMS can be expected, based on the findings that right prefrontal rTMS could induce feelings of happiness and hypomania in healthy volunteers (Grisaru et al. 2001). An open and prospective study applying right prefrontal high frequency (20 Hz) rTMS at 80% motor threshold for 4 weeks as an add-on treatment in eight manic bipolar I in-patients showed a sustained reduction of manic symptoms in all patients (Michael and Erfurth 2004). One 2-week study compared left to right prefrontal high frequency (20 Hz) rTMS, administered with a circular electrode at 80% MT in 16 manic patients. Significantly more improvement of manic symptoms was observed in patients treated with right than with left prefrontal 20 Hz rTMS. The left-sided stimulated group however was a more seriously ill population (Grisaru et al. 1998a; McNamara et al. 2001). The same researchers recently published a study (Kaptan et al. 2003), in which 19 manic patients completed a sham-controlled trial for right prefrontal rTMS with the same parameters (20 Hz, 800 pulses per day, 80% MT). There were no significant differences between the active and sham stimulation. The authors conclude that right-sided stimulation may not be an issue, but rather that left-sided stimulation would worsen mania. A report by Nedjat and Folkerts (1999) in which left-sided stimulation at high frequency in-

duced hypomania could support this hypothesis (Kaptan et al. 2003).

Anxiety disorders

Neurobiological models of obsessive–compulsive disorder (OCD) state that disturbances in the cortico–striato–pallido–thalamic pathways, including the prefrontal cortex, play a central pathophysiological role. Functional imaging, pharmacological interventions and neurosurgical interventions show evidence for a possible frontal hyperactivity in OCD (George et al. 2002). Studies with paired pulse TMS support the hypothesis of a decreasing intracortical inhibition (Greenberg et al. 1997, 2000a; Ziemann et al. 1997; Cora-Locatelli et al. 1998; Sachdev et al. 2001; Burt et al. 2002). The effects of prefrontal rTMS in OCD have been investigated in a small number of trials. Martin et al. (2003b) published a systematic review for the Cochrane database. Only three randomised controlled trials could be included and it was not possible to pool any results for meta-analysis. There was no difference between rTMS and sham rTMS. Low frequency rTMS trials resulted in no effect at all (Alonso et al. 2001). A beneficial but unclear significant effect of right prefrontal high frequency rTMS was observed (decrease of compulsive urges for several hours).

A prefrontal, limbic and paralimbic activation is suspected in the pathophysiology of PTSD. Prefrontal rTMS was applied in a few rTMS trials including in total 20–30 patients (Grisaru et al. 1998b; McCann et al. 1998; George et al. 2002; Cohen et al. 2004). There was some success with right but not left prefrontal low frequency (1 Hz) rTMS (Greenberg et al. 2000b; Rosenberg et al. 2002). One small study with 10 patients produced some encouraging results. After a 30-s lasting stimulus at 0.3 Hz over both motor cortex regions (15 min each) a mild and transient diminished avoidance, anxiety and somatisation were experienced (Grisaru et al. 1998b; Burt et al. 2002). The same research group conducted a 2-week placebo-controlled blind trial including 24 patients. They found a marked greater improvement in PTSD core symptoms (re-experiencing, avoiding and hyper arousal) with right dorsolateral prefrontal 10 Hz rTMS at 80% MT, compared to low frequency or sham stimulation (Cohen et al. 2004).

Psychotic disease

Beneficial effects of rTMS on psychosis as a whole have not been observed until today (Klein et al. 1999; McNamara et al. 2001). Psychotic depression

does not respond as well to rTMS as to ECT. Two treatment-resistant depressed females developed psychotic symptoms with high frequency rTMS over the left prefrontal cortex. The symptoms resolved after discontinuing rTMS (Conca et al. 2002). Zwanzger et al. (2002) reported the occurrence of recurrent severe delusions in one nonpsychotic depressed patient treated with rTMS. A possible explanation is the enhancement of dopaminergic neurotransmission caused by rTMS (Strafella et al. 2001, 2003).

There is one symptom of psychosis, namely hallucinations, which can be the target for rTMS because it originates from brain regions in reach of the magnetic field: imaging studies show activation in the right and left superior temporal cortex, Brocca's area and the left temporo-parietal region of people suffering from acoustic hallucinations (Hoffman et al. 2003). In a first clinical trial, a statistically significant improvement was observed on a hallucination scale after 10 days of rTMS at the left auditory cortex in nine medication-resistant hallucinating patients (d'Alfonso et al. 2002). In two double-blind sham-controlled trials low frequency (1 Hz) rTMS over the left temporo-parietal cortex produced a decrease in acoustic hallucinations over time in 36 schizophrenic patients. A substantial part of the responders (52%) showed sustained improvements at 15 weeks follow-up. They also paid significantly less attention to the hallucinations (Hoffman et al. 2000, 2003).

Dependence and abuse

Acute high frequency frontal rTMS has efficiently modulates the mesostriatal and mesolimbic dopaminergic reward system in both animals and humans. For this reason, Eichhammer et al. (2003) studied the effects of left prefrontal high frequency (20 Hz) rTMS in 14 nicotine-dependent patients. Cigarette smoking but not levels of craving decreased significantly.

Limitations of TMS

Safety and tolerability

Single and repetitive pulse TMS are well tolerable. An occasional local, mild muscle tension headache and muscular twitching at the stimulation site can occur. The burden caused by the loud clicking sound is resolved by using foam earplugs, which are also effective to prevent cochlear lesions (Barker et al. 1985; George et al. 1999; Fitzgerald et al. 2002).

The most important safety matter is the risk of seizure in the conscious patient. Single-pulse TMS is generally considered safe, but rTMS has a (theoretically) higher risk of seizures because of the higher amount of administered energy to the brain. In the literature, only 12 seizures during rTMS have been described since 1985 (George et al. 2002). None of these cases mentioned any irreversible or persistent sequels. Stimulation with parameters far above current safety thresholds had to be used to induce therapeutic seizures in one study (Lisanby et al. 2001). Safety guidelines were published by Wassermann in 1998 (Table IV) and were mainly developed to minimise the risk of convulsions. Important concerns in the safety regulations are the shape of the stimulation coil, the stimulation site, the administered energy, total number of stimuli and trains per day, the length of treatment. Stimulation frequency itself also has its limits, as frequencies higher than 25–30 Hz increase seizure risk (George et al. 2002). The occurrence of two documented seizures since 1998 within these first safety limits needed extra criteria for minimal safe interval duration between stimuli trains (Chen et al. 1997b). To reduce the risk of seizures, high frequency rTMS should be applied only in short pulse series, with relatively long impulse-free intervals (20 s). All researchers followed these safety guidelines over the past 4 years and inadvertent seizures did not occur. Patients taking medications that decrease the convulsive threshold, like tricyclic antidepressants or antipsychotics, also showed no higher risk in recent studies (Wassermann 1998, 2000).

Table IV. Safety guidelines: maximum safe duration (seconds) for single trains of rTMS (from Wassermann 1998).

Frequency (Hz)	Intensity (% MT)													
	100	110	120	130	140	150	160	170	180	190	200	210	220	
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6	
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2	
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3	
20	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1	
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08	

The second important safety matter is the influence of rTMS on cognition. Cognitive effects of rTMS have been investigated using a variety of means. Transient disruption of cognition is a well-recognised effect of stimulation at certain brain sites, but enhanced function is reported in other domains (Fitzgerald et al. 2002). According to recent reviews (George et al. 2002; Fitzgerald et al. 2002), and studies published since then (O'Connor et al. 2003), no deleterious cognitive side effects were described after courses of rTMS (Little et al. 2000). Several studies point out that there would even be a possible shortening of motor reaction time and an improved visual memory after rTMS. Evidence of modest but statistically significant improvement in performance in working memory-executive function, objective memory and fine motor speed domains over the rTMS treatment period is growing, as illustrated by a study of Martis et al. (2003). Other studies do not show important changes in the diverse cognitive functions after chronic and repetitive TMS (over a period of several years). Some warn of possible disturbances, especially when administering rTMS with high intensity and short intervals over longer-lasting stimulation periods.

A final important safety issue is the risk of shift into a manic or psychotic state when treated for depression. Some reports observed shifts into mania after high frequency left prefrontal rTMS and low frequency right prefrontal rTMS (Garcia-Toro 1999; Nedjat and Folkerts 1999; Dolberg et al. 2001; Ella et al. 2002; Fitzgerald et al. 2003; Sakkas et al. 2003). However, this concerned only a few individuals. Several other trials in healthy volunteers and bipolar patients observed no changes (Nahas et al. 2003). Induction or worsening of psychotic symptoms was a reason for dropout in three patients from different studies (Conca et al. 2002; Shajahan et al. 2002). Considering the amount of available studies and the large amount of patients who underwent rTMS in the past decade, these reports are rather marginal.

No long-term adverse effects have been observed since the development of this technique in 1985. Histopathological research in animals undergoing rTMS showed no pathological findings. Human MRI studies confirmed that gross brain structures remain intact. Theoretically, one could expect tissue lesions caused by a massive hyperexcitation of the neurons or tissue heating. Current TMS devices, however, have in-built safety standards that protect neurons against massive neuronal excitation (Fitzgerald et al. 2002).

Hypothetically, exposure to static magnetic fields can have biological effects. Continuous exposure (such as in MRI and in the surroundings of high-

tension cables) is without any risk (National Research Council, Washington 1996; Verkasalo et al. 1996). TMS does not produce magnetic fields for such a long period, but they are more powerful and little is known about risks of repetitive exposure of focal identical tissue zones to TMS. Until today, no reproducible harmful effects were described.

Contra-indications

Any risk factor for seizure, such as pre-existent epilepsy, comorbid drug or alcohol abuse and the presence of intracranial processes and other causes of elevated intracranial pressure are contra-indicated. Because of interaction with the magnetic field, the presence of larger metal objects with high conductance and ferromagnetic properties in the head or eyes, implanted electronic devices and intracardial conduction wires are contra-indicated. Also, objects outside, but close to the person, such as magnetic credit cards, floppy disks, electronic devices and watches have to be taken away. Pregnancy is another contra-indication, not for the mother (Li et al. 2002) but because very little is known about TMS effects on the brain of a developing foetus.

Questionable usefulness in the elderly

One can presume that the distance between cortex and skull surface increases in elderly patients due to a certain amount of cortical atrophy. Because the magnetic field declines with increasing distance from the stimulation coil these patients would benefit less from rTMS. Functional imaging supports this hypothesis (Nahas et al. 2001b).

In a small depressed patient sample rTMS responders were significantly younger ($P=0.026$), with distances from coil to prefrontal cortex lower than 17.00 mm (Kozel et al. 2000). Such findings were replicated in healthy volunteers (McConnell et al. 2001). We only found one small rTMS trial studying older depressed patients (mean age 60.7 years). There was no significant difference between groups pre- or post-treatment but the three responders had significantly greater frontal lobe volume than non-responders, supporting the formulated hypothesis (Manes et al. 2001).

Discussion

In the last decade, TMS research has developed enormously. From the viewpoint of the neuroscientist, TMS is a methodology with great potential as a research tool (Gershon et al. 2003; Schlaepfer et al. 2003). For clinical psychiatrists it is also a very attractive tool because it is a safe and patient-friendly

procedure when applied according to the standardised safety guidelines. A few trials have studied its potential in psychosis, OCD and PTSD, showing some preliminary positive effects. Most energy has been dedicated to the use of rTMS in mood disorders. Some promising results have been observed, but major uncertainties remain. There is no consensus about the exact mechanisms of action of how rTMS might induce antidepressant effects, but this is also the case for other antidepressant treatments. Most conclusions were drawn from trials with small patient samples, lacking real double-blind control and with short duration (2 weeks). Effect sizes in a small number of meaningful trials are modest and variable. Sources of this lack of concordance between studies include differences in stimulation parameter settings, the use of concomitant medications and different characteristics of patient samples. Ideal and reproducible coil placement localisation is also subject to debate. The magnitude of the antidepressant effect, while often statistically significant, has been below the threshold of clinical usefulness (Schlaepfer et al. 2003). Effects also were of short duration. The authors of the most critical meta-analysis conclude that there is currently insufficient evidence to suggest that rTMS is effective in the treatment of depression, but they do not want to exclude the possibility that rTMS may be of benefit (Martin et al. 2003c).

Although these conclusions do not sound very encouraging, there should be no reason to abandon rTMS in affective disorders. Many of the current successful psychiatric treatments have developed slowly, going through a process of initial enthusiastic approval followed by almost total demise and then back to sensible, widespread use (Martin et al. 2003c). Moreover, recent preclinical animal studies showed important genetic and molecular changes emphasising rTMS cellular activity. Functional cerebral imaging during rTMS-stimulation seems promising in order to understand better rTMS mechanisms. In clinical trials, there were comparative effects of ECT and rTMS and the development of magnetic seizure therapy (MST) seems promising for the efficacy of rTMS, at least in some subtypes of affective disorders.

Our actual knowledge concerning the usefulness of rTMS in the treatment of psychiatric disorders should stimulate and justify further new high-quality preclinical and clinical research. One limitation, however, is the difficulty in obtaining the necessary important financial funds (Padberg and Möller 2003; Schlaepfer et al. 2003).

New research should focus on the need for ideal uniformed technical parameters and the study of longer-lasting treatment regimens with special

attention to the continuation treatment and prevention phase. Larger patient groups with more precisely described psychopathology should be included and studies should be double-blind, real sham-controlled and multi-centre organised.

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

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REVIEW

Antioxidative and steroid systems in neurological and psychiatric disorders

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Abstract

A large number of neurological and psychiatric diseases like Morbus Parkinson, amyotrophic lateral sclerosis, dementia, schizophrenia and probably also affective disorders show an enhanced production of reactive oxygen species. Moreover, alterations of antioxidative systems and beneficial effects of antioxidative substances including steroid compounds such as estrogens have been described in several of these diseases. This review focuses on alterations of antioxidative systems in the course of neurological diseases and psychiatric disorders and on the differential effects of steroids on these systems in the central nervous system. Moreover, a possible clinical relevance of alterations of circulating steroids and of steroid treatment under these conditions is discussed.

Key words: *Antioxidative systems, neurological and psychiatric disorders, steroids*

Introduction

An enhanced production of reactive oxygen species like the superoxide and the hydroxyl radical or hydrogen peroxide occurs in a number of neurological and psychiatric disorders. For example, an enhanced formation of reactive oxygen species (ROS) has been described in amyotrophic lateral sclerosis (Cookson and Shaw 1999), Alzheimer's disease (Markesbery and Carney 1999), Duchenne muscle dystrophy (Ragusa et al. 1997), cerebral ischemia (Love 1999), Down's syndrome (Busciglio and Yankner 1995), epilepsy (Frantseva et al. 2000), Huntington's disease (Brown et al. 1999), Parkinson's disease (Jenner 1998), schizophrenia (Smythies 1997) and neuroAIDS (for review, see Mollace et al. 2001) as well as in animal models of brain injuries (for review, see Lewen et al. 2000), of spinal cord injuries (Liu et al. 1998) and in a cell culture model of experimental prion disease (Milharet et al. 2000). A first study on antioxidant reserve and oxidative injury in clinically examined brain traumas demonstrated an enhanced free radical-mediated lipid peroxidation (Bayir et al. 2002). The context between ethanol and oxidative mechanisms in the brain was reviewed by Sun and Sun (2001) and effects of amphetamines on radical

formation and on oxidative stress were described by Brown and Yamamoto (2003).

The brain is much more vulnerable to reactive oxygen compounds than other tissues, since it utilizes 20% of the oxygen consumed by the body, although it comprises only 2% of the body weight (Clarke et al. 1999). Moreover, the central nervous system (CNS) has a high iron content (Gerlach et al. 1994) and contains an abundance of polyunsaturated fatty acids (Dringen et al. 2000), the target of lipid peroxidation. Furthermore, the brain shows a rather low concentration of antioxidant enzymes in contrast to peripheral organs like the kidney or the liver (Cooper 1997). On the other side, antioxidative mechanisms have been considered in the treatment of CNS diseases, underscoring the clinical relevance of the issue (Floyd and Hensly 2002; Riecher-Rössler 2002; Vedder and Behl 2003). Overall, the data strongly support the assumption that pro- and anti-oxidative mechanisms may be primarily or secondarily involved in the pathology of CNS diseases.

Alterations of antioxidant systems in neurological and psychiatric disorders

In a large number of diseases and in the natural process of aging, alterations in the activity of

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antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) or glutathione peroxidase (GPx) have been extensively discussed in the literature, even with special regard to the CNS. Additionally, lowered levels of substances with antioxidative capacity like glutathione (GSH) or vitamin E have been demonstrated in the CNS or in peripheral body components like plasma or red blood cells in several diseases.

In sporadic amyotrophic lateral sclerosis Przedborski et al. (1996) demonstrated a significantly reduced GPx activity in the precentral gyrus of the cerebral cortex, a region affected in the disease. In the context of cerebral ischemia, Mizui et al. (1992) described an enhanced extent of cerebral ischemic injury after depletion of brain GSH by buthionine sulfoximine in the rat. After hypoxic ischemia, Wallin et al. (2000) demonstrated decreased GSH levels in the mitochondrial fraction and in the tissue of the ischemic hemisphere.

Regarding alterations of the antioxidative system in the context of Parkinson's disease, a significant decrease of 40% of the GSH levels in the substantia nigra has been shown by Jenner et al. (1992). The GSH content was also significantly decreased in pooled samples of putamen, globus pallidus, substantia nigra, the nucleus basalis of Meynert, the amygdaloid nucleus, and the frontal cortex of parkinsonian brains with severe damage to substantia nigra (Riederer et al. 1989), whereas no significant alterations of GSH levels were observed in the substantia innominata or the cingulate cortex (Gu et al. 1998). Kish et al. (1985) reported a decrease of approximately 20% of GPx activity in the substantia nigra, the external globus pallidus, the putamen, and the frontal cortex of Parkinsonian brains compared to the brains of controls, whereas Marttila et al. (1988) found no differences in different brain regions and the cerebrospinal fluid in a similar study. Kunikowska and Jenner (2003) examined alterations in the mRNA expression of Cu, Zn-SOD and GPx in the basal ganglia in an animal model and in patients with Parkinson's disease. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated marmosets, significantly decreased Cu, Zn-SOD mRNA levels have been described in the pars compacta of the substantia nigra and in other regions (nucleus accumbens, caudate nucleus, putamen, globus pallidus), whereas the levels were unchanged in the pars reticulata of the substantia nigra. In contrast, GPx mRNA levels showed no significant alterations in the examined areas of the animals. In patients with Parkinson's disease, the authors found significantly decreased Cu, Zn-SOD mRNA levels in the pars compacta compared to control tissues, but unchanged levels in the pars

reticulata. Furthermore, they detected a complete loss of GPx mRNA in the pars compacta and a severe loss in the pars reticulata. It has to be mentioned that the activity of Cu, Zn-SOD in the substantia nigra was unchanged in Parkinson's disease (Poirier et al. 1994), whereas the activity of Mn-SOD was increased in the substantia nigra (Saggi et al. 1989). In a recent study, Power et al. (2002) demonstrated a significant increase of non-selenium GPx-positive glial cells in the grey and white matter of the frontal cortex in Parkinson's disease. Nonselenium GPx is a recently identified novel antioxidative enzyme. Furthermore, alterations of selenium, an antioxidant and a component of GPx, have been described in the context of Parkinson's disease in cerebrospinal fluid of non-levodopa-treated patients (Aguilar et al. 1998). In these patients, selenium levels were significantly increased.

Alterations of the GSH system have also been observed in Down's syndrome (Stabel-Burow et al. 1997), epilepsy (Müller et al. 2001), Huntington's disease (Sian et al. 1994), multiple-system atrophy (Sian et al. 1994) and progressive supranuclear palsy (Sian et al. 1994).

In progressive supranuclear palsy, a parkinsonian movement disorder, Cantuti-Castelvetri et al. (2002) demonstrated significantly elevated GSH levels in the cerebellum, the subthalamic nucleus, the globus pallidus, the calcarine cortex and the frontal cortex. Furthermore, they found significant increases in the activity of Cu, Zn-SOD in the calcarine cortex and other brain areas (caudate nucleus, subthalamic nucleus, globus pallidus, frontal cortex, and the cerebellar cortex), whereas Mn-SOD activity was significantly increased in the subthalamic nucleus only.

Regarding alterations in the activity of antioxidant enzymes in traumatic brain injury, Goss et al. (1997) described elevated GPx and CAT activities. In the context of spinal cord injuries, the results are not clear: Azbill et al. (1997) detected significantly increased GSH levels in their study, whereas Kamencic et al. (2001) found a reduced GSH content in animal models of spinal cord injury. Azbill et al. (1997) also described an increased CAT activity after spinal cord injury.

Beside some examinations in peripheral systems, a lot of studies show alterations in the activity of antioxidant enzymes in various brain regions in dementia of the Alzheimer type. Aksenov et al. (1998) found elevated levels of CAT, GPx and glutathione reductase (GR) mRNA in the hippocampus and the inferior parietal lobule, but not in the cerebellum of Alzheimer patients. Chen et al. (1994) described a significantly lower SOD activity

in the cerebellum, the frontal cortex and the hippocampus, whereas no significant differences in CAT activity were detectable. Gsell et al. (1995) examined alterations in the activities of SOD and CAT in the basal ganglia, cortical and limbic brain regions of Alzheimer brains. The activity of CAT was significantly reduced in the parietotemporal cortex, in the basal ganglia and in the amygdala, whereas SOD activity showed no alterations. Lowell et al. (1995) investigated alterations of antioxidative enzyme activity in various brain regions of Alzheimer's disease brains: GPx activity was significantly increased in the hippocampus, the amygdala and the piriform cortex. In the hippocampus and in the amygdala, the authors found significantly increased activities. CAT activity was significantly increased in the hippocampus and in the superior and middle temporal gyri, while SOD activity was enhanced in all brain regions studied (amygdala, hippocampus, piriform cortex, superior and middle temporal gyri, inferior parietal lobule, middle frontal gyrus, occipital pole and cerebellum). In a further study, Lowell et al. (1998) demonstrated significantly decreased glutathione-S-transferase (GST) activities in the amygdala, the hippocampus, the parahippocampal gyrus, the inferior parietal lobule and in the nucleus basalis of Meynert. In the study of Marcus et al. (1998), the authors demonstrated significantly reduced activities of SOD in the frontal and in the temporal region. In the latter region, the activity of CAT was also significantly decreased. In context with selenium, Cornett et al. (1998) described an increase of the element in the amygdala and Wenstrup et al. (1990) reported a decrease of selenium levels in the temporal lobe.

Within the scope of other psychiatric disorders like major depression, bipolar disorders, obsessive-compulsive disorders, panic disorder or schizophrenia, only alterations of the antioxidant components in peripheral systems have been described: Bilici et al. (2001) examined activities of antioxidant enzymes in plasma and erythrocytes of patients with major depression with and without melancholia. Plasma GR levels were significantly increased in depressed patients with melancholia compared to controls, whereas GPx showed no alterations in both groups of patients. In erythrocytes of the patients with melancholia, activities of GPx and SOD were significantly increased, while, in patients without melancholia, only SOD activity was significantly higher. CAT activities, however, were not altered. Maes et al. (2000) described significantly lower serum concentrations of vitamin E in patients with major depression. Srivastava et al. (2002) found no alterations of the activities of SOD, CAT and GPx in polymorphonuclear leukocytes from patients with

depression. Kuloglu et al. (2002a) determined the activities of antioxidant enzymes in hemolysates of erythrocytes of patients with obsessive-compulsive disorder with and without depressive disorder. Compared to a control group, SOD activity was significantly higher in the group with the comorbidity of a major depression. The activities of GPx were significantly increased in both groups, whereas CAT activity showed no significant alterations.

In a further study, Kuloglu et al. (2002c) examined activities of antioxidative enzymes in hemolysates of erythrocytes of patients with schizophrenia and bipolar disorder. SOD activity was significantly enhanced in both groups, whereas GPx was significantly higher in the schizophrenic group only. Furthermore, the authors demonstrated significantly higher activities of GPx and SOD in erythrocyte hemolysates of patients with panic disorder (Kuloglu et al. 2002b), while CAT activity was not significantly altered.

In the context of schizophrenia, altered levels of antioxidative enzymes have been discussed in a number of publications, although in part controversially: Mukherjee et al. (1996) demonstrated a significant lower SOD activity in red blood cells of drug-naïve patients. GPx and CAT activities, however, showed no significant differences. These results were confirmed by a study of Yao et al. (1998). Zhang et al. (2003) demonstrated an increased activity of whole blood SOD in neuroleptic-free schizophrenia patients compared to controls. Srivastava et al. (2001) examined antioxidant enzyme levels in polymononuclear leukocytes of anti-psychotic drug-free schizophrenic patients. Activities of GPx and SOD showed no significant alterations and the detected increase in CAT activity was statistically not significant. The only examination in the CNS in this context was the study of Do et al. (2000): the authors described a significant decrease of GSH levels in the cerebrospinal fluid and also in the medial prefrontal cortex of drug-free schizophrenic patients.

Pharmacological influences on antioxidative compounds

In addition to these studies in schizophrenia, mainly performed on neuroleptic-free patients, effects of neuroleptics on antioxidant enzyme activities have been shown in animal and human models: besides some studies in animals (Szabo et al. 1983; Roy et al. 1984; Murthy et al. 1989; Cadet and Perumal 1990), Parikh et al. (2003) examined the effects of the neuroleptics clozapine, haloperidol, olanzapine and risperidone on the activities and contents of antioxidant enzymes in rat brains. Mn-SOD as well

as Cu, Zn-SOD activity and content were significantly reduced after a 45- and a 90-day treatment with haloperidol. CAT activity and content were significantly decreased after a 45-day treatment, while GPx activity showed no alterations. Furthermore, administration of haloperidol to rats decreased the level of reduced GSH (Shivakumar and Ravindranath 1993). In humans, such effects have also been discussed (Reddy et al. 1992, 1993). Under similar conditions, Yao et al. (1998) only observed a significantly lower erythrocyte SOD activity after treatment with haloperidol.

Regarding effects of alcohol abuse on antioxidative systems, alterations of antioxidative compounds have been mostly studied in animal models: Montoliu et al. (1994) described a significantly enhanced ROS formation in rat brain homogenates after chronic alcohol exposure, whereas the general context between ethanol and oxidative mechanisms in the brain was reviewed by Sun and Sun (2001). In men, Götz et al. (2001) examined Cu, Zn-SOD, Mn-SOD and CAT activities as well as GSH levels in several brain regions of post-mortem brains of patients with alcohol abuse. They described a slight, but significantly increased activity of CAT in the frontal cortex and a significantly decreased CAT activity in the corpus callosum of alcohol-dependent patients. Both forms of the SOD showed no significant alterations. GSH was significantly elevated in the corpus callosum and in the amygdala of patients compared to the control brain regions. Furthermore, the authors demonstrated a nearly two-fold increase of oxidized GSH in the frontal cortex, in the corpus mamillaria, in the cerebellum, and in the nucleus accumbens.

In the context of heroin abuse, Zhou et al. (2000) determined levels of vitamin C and E in the plasma and the activities of antioxidant enzymes in erythrocytes of heroin abusers. The average plasma values of the vitamins C and E and the average erythrocyte values of SOD, CAT and GPx were significantly decreased in heroin abusers. Formation of ROS after heroin treatment was described by Oliveira et al. (2002) in undifferentiated PC12 cells and cocaine was shown to increase hydroxyl radical formation in brains of chicken embryos (Castelli et al. 2001).

Regarding the influence of other drugs on antioxidative systems, Jayanthi et al. (1998) examined the effects of methamphetamine on cortical and striatal antioxidant systems in non-transgenic and SOD-transgenic mice. Treatment with methamphetamine led to a significant decrease in Cu, Zn-SOD activity in the cortical region without alterations in striatal activity in non-transgenic mice. Furthermore, methamphetamine induced a significant decrease in CAT activity in the striatum. In

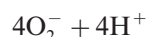
addition, methamphetamine caused significant decreases in GPx activity in both regions of non-transgenic mice. In a further study, Jayanthi et al. (1999) described alterations in the activities of antioxidant enzymes caused by methylenedioxy-methamphetamine (MDMA, 'Ecstasy') in SOD-transgenic and non-transgenic mice. Treatment with MDMA led to significant decreases in enzyme activity of Cu, Zn-SOD in the examined brain regions (frontal cortex, caudate putamen and hippocampus) in non-transgenic mice. CAT activity was significantly lower in the caudate putamen and in the hippocampus of non-transgenic mice and the activity of GPx was significantly decreased in the frontal cortex only. In erythrocytes of ecstasy abusers, Zhou et al. (2003) demonstrated significantly decreased average values of SOD, CAT and GPx. Carvalho et al. (2001) examined effects of repeated administration of *d*-amphetamine on antioxidative enzymes in rat brain: GST activity was enhanced in the hypothalamus and the activity of GPx was increased in the striatum, in the nucleus accumbens and in the medial prefrontal cortex. GR activity was enhanced in the hypothalamus, but decreased in the medial prefrontal cortex. Furthermore, the authors described an increase of CAT activity in the medial prefrontal cortex after repeated *d*-amphetamine treatment. In a first study, Acikgöz et al. (1998) showed a significant increase of SOD activity in the rat striatum after repeated administration of methamphetamine, whereas the treatment caused no changes in GPx activity. The authors observed the same results after chronic administration of methamphetamine. In a second study, Acikgöz et al. (2000) found a significant increase of SOD activity in the prefrontal cortex of the rat after a single dose of methamphetamine. Within the scope of their study, Goudas et al. (1997) demonstrated that a systemic application of morphine exerted no significant effects on the concentration of reduced GSH in selected brain areas. Moreira et al. (2003) demonstrated in their study, that apomorphine increased CAT, but not SOD activity in the mice forebrain. Treatment with 8-oxo-apomorphine-semiquinone (8-OASQ) resulted in a specific dose-dependent increase of CAT activity, whereas SOD activity was not affected.

In summary, alterations of antioxidant systems have been described in almost all important neurological diseases as well as in psychiatric disorders and in many forms of drug abuse, although often only in peripheral organ systems. Despite these data, interactions between the different antioxidant enzymes under conditions of clinical disease have rarely been examined. Unfortunately, this also includes aspects of reciprocal compensation and other types of

differential regulation under different treatment conditions including application of steroid hormones.

Neuropsychopharmacology of steroid hormones

The clinical use of steroid hormones in many of the above-mentioned diseases and disorders is partially well established and partially controversially discussed. For example, systemic administration of the synthetic glucocorticoid 6-methylprednisolone (6-MP) is a standard part of the therapy of spinal cord injury (Bracken et al. 1997), as is the use of the synthetic glucocorticoid dexamethasone in the treatment of tumor-induced brain edema (for review, see Koehler et al. 1995). The use of estrogens in the treatment of Alzheimer's disease (for review, see, for example, Fillit 2002), Parkinson's disease (for review, see, for example, Tsang et al. 2001), cerebral ischemia (for review, see Paganini-Hill 2001), depression (Grigoriadis and Kennedy 2002) and schizophrenia (Riecher-Rössler 2002) is discussed. Despite these clinical implications, the underlying preclinical mechanisms have yet rarely been identified, although antioxidative actions may play a significant role in this context (Behl 1997, 1999; Culmsee et al. 1999; Vedder et al. 1999; Vedder and Behl 2003). Therefore, we here focus on the effects of steroids on antioxidative components as an emerging action of steroids in the CNS.



Effects of steroid hormones on antioxidative compounds in the central nervous system

Although a number of studies have shown antioxidative actions of glucocorticoids (Behl 1998; for review, see McIntosh and Sapolsky 1996) and antioxidative effects of estrogens in the context of CNS illnesses (for example, see Behl 1997, 1999; Vedder and Behl 2003), only a very small number of studies deals with the effects of steroids on the different antioxidative compounds in the CNS in detail.

This is especially noteworthy, since numerous studies have described the effects of steroid hormones on antioxidative compounds in various peri-pheral organ systems. Such actions, however, might be of great pharmacological interest because of alterations of the antioxidative systems reported in neurological diseases and psychiatric disorders.

In a first study, Ahlbom et al. (1999) found an increased CAT activity and no significant differences in the amount of GSH in cerebellar granule neurons

of the rat after testosterone treatment *in vitro*. In a further examination, Ahlbom et al. (2000) demonstrated that high levels of dexamethasone exerted a long-lasting decrease of CAT activity in rat cerebellar granule cells *in vitro* and *in vivo*. McIntosh et al. (1998) examined effects of physiological concentrations of corticosterone on antioxidant enzyme activities in the hippocampus, cortex and cerebellum of the rat. They were able to show a significantly reduced Cu, Zn-SOD activity in all brain regions examined. The activity of GPx was significantly decreased in the hippocampus and in the cortex, while other enzymes showed no significant alterations. The study of Patel et al. (2002) examined effects of corticosterone on GSH levels and GPx activity in rat hippocampal cultures. They described significantly decreased levels of GSH in the presence of 20 mM glucose and a concomitant treatment with corticosterone. The steroid also caused a small, but significant decrease in GPx activity. In our laboratory, we examined the effects of glucocorticoids and gonadal steroids on GSH levels in mouse neuronal (HT22) and rat glial (C₆) cell lines as well as in primary rat hippocampal and neocortical cultures (Schmidt et al. 2002). With regard to the effects of steroids on GSH levels, three important aspects have to be mentioned: first, 17 β -estradiol (E₂) (10⁻⁷ M) treatment led to significant increases in the amounts of GSH in all cell types after long-term (24 h) treatment; second, the highest increase of GSH levels measured was observed in hippocampal HT22 cells after long-term incubation with the synthetic glucocorticoid 6-MP (10⁻⁷ M); and third, the physiological glucocorticoid of the rodent, corticosterone, exerted effects in the glial cell line only. In a further study (Schmidt et al. 2005), we investigated the effects of glucocorticoids and gonadal steroids on CAT activity in HT22 and C₆ cells. In contrast to the cell-specificity of the GSH effects, corticosterone here acted on both, the neuronal and the glial cell line. Furthermore, long-term effects of glucocorticoids on CAT activity were not detectable. With regard to GSH, gonadal steroids exerted both, short- and long-term effects, in neuronal HT22 cells. The comparison between neuronal and glial cell lines in this context was important, because glial cells have been demonstrated to protect neurons in culture from toxic insults (Desagher et al. 1996).

Implications of the effects of steroid hormones on antioxidative compounds in the central nervous system

The effects of steroid hormones on antioxidative systems in the CNS are of great clinical and also of

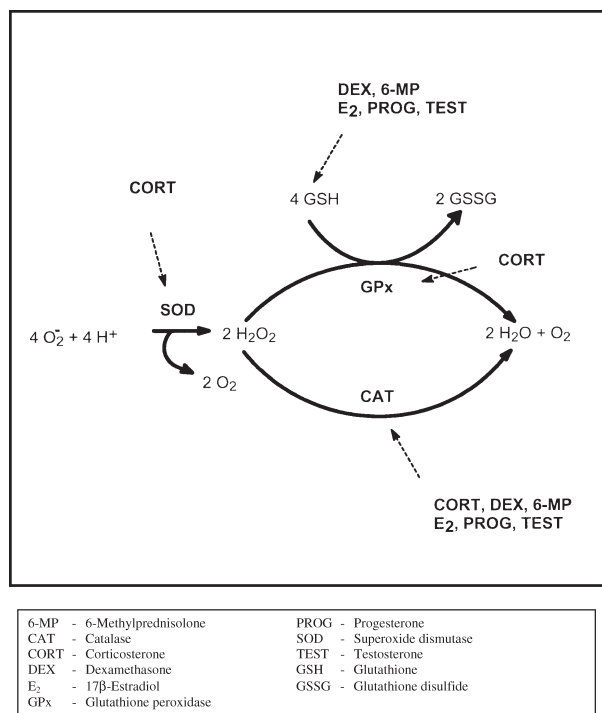


Figure 1. Effects of steroid hormones on antioxidative compounds in the central nervous system (Schmidt et al. 2005).

pathophysiological relevance from the perspective of neuroendocrine alterations in a number of neurological diseases and psychiatric disorders, the numerous alterations of the antioxidant systems in CNS diseases, of the various therapeutic applications of steroids discussed above and also in regard to further treatment options in a number of illnesses.

For example, the context between the use of 6-MP in the treatment of spinal cord injury (Bracken et al. 1997) and the described alterations in the amount of GSH in traumatic injuries (Azbill et al. 1997; Kamencic et al. 2001), as well as the effects of 6-methylprednisolone treatment on GSH levels in hippocampal HT22 and primary hippocampal neurons observed in our laboratory, point to an important role of the specific actions of 6-MP on the regulation of antioxidative compounds like GSH in the CNS under pathological conditions.

Furthermore, the toxicity of amyloid β protein, a peptide which accumulates in plaques of Alzheimer's disease brains, is mediated by hydrogen peroxide (Behl et al. 1994). Interestingly, amyloid β -toxicity-resistant cells had higher mRNA and protein levels of CAT and GPx as well as higher antioxidative enzyme activities (Sagara et al. 1996). In our laboratory, we showed that long-term (24 h) incubation with E₂ significantly increases the amounts of GSH in all cell lines and primary cultures investi-

gated (Schmidt et al. 2002), pointing to a possible relevant underlying mechanism. Since GSH levels are affected in Alzheimer's disease, estrogen-induced alterations of antioxidative compounds such as GSH may be involved in the beneficial actions of these hormones. This would also be in line with the clinical result that estrogen levels are decreased in cerebrospinal fluid and inversely correlated with increased levels of amyloid β in affected Alzheimer patients (Schönknecht et al. 2001). Taken together, these results suggest a plausible link between the preclinical and clinical results of the effects of estrogens with regard to antioxidant systems including GSH in Alzheimer's disease.

Moreover, estrogens have been demonstrated to affect the manifestation and also the pathophysiology of schizophrenia (Riecher-Rössler 2002). The detailed underlying mechanisms are rather unclear at the moment, although antioxidative effects of estrogens in general have been suspected to be involved in the course of the disorder (Vedder and Behl 2003). In view of the result that GSH deficiency in the prefrontal cortex may play an important role in the disease, as has been shown by Do et al. (2000) in untreated schizophrenic patients, and that estrogens increase GSH levels in a number of preclinical CNS model systems (Schmidt et al. 2002), the latter preclinical mechanism may at least partially explain the beneficial effects of estrogens in schizophrenia.

Very recently, alterations of GSH levels have also been shown in major depression (Bilici et al. 2001). With regard to our results on a decrease of GSH levels evoked by corticosterone after long-term (24 h) treatment (Schmidt et al. 2002) and to the data on increased levels of cortisol in major depression (e.g., Plotsky et al. 1998; Holsboer 2001), neuroendocrine-antioxidative interactions may play a significant role in major depression and other diseases. This is further substantiated by the effects of antidepressants on antioxidative parameters (Bilici et al. 2001). Moreover, previous results indicate that the metabolism of certain estrogens, the so called catecholestrogens (Banger et al. 1990), is pathologically altered in major depression. As has recently been shown by our group (Teepker et al. 2003), catecholestrogens such as 2-OH estradiol have potent antioxidative properties in CNS systems, pointing to the possibility, that estrogens and especially catecholestrogens may exert neuroprotective effects in major depression and probably also other CNS diseases. On the other hand, it has to be mentioned and considered that catecholestrogens are also able to act as pro-carcinogens under certain conditions (for review, see Liehr 1997).

In conclusion, at the moment only few data exist from an emerging field in neuroscience, e.g., the interactions between steroid compounds, the neuroendocrine and the antioxidative system in the CNS. Because of the obvious medical relevance, preclinical as well as clinical studies are urgently required to elucidate the participating mechanisms and the conditions of clinical applications in more detail.

Acknowledgements/Statement of interest

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ORIGINAL INVESTIGATION

Frequency and characteristics of recurrent major depressed patients with unimpaired executive functions

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Abstract

Major depression is associated with impairment of cognitive functions, and especially higher-order cognitive processes referred to as executive functions (EF). Whether this is a general finding is unclear. Patients without EF impairment may have different treatment needs than patients with EF impairment, and will probably have a better everyday functioning. Thus, it is important to identify the prevalence and characteristics of depressed patients without EF impairment. Forty-three patients with recurrent major depressive disorder (19–51 years) and 50 healthy controls were included in the study. The subjects were assessed with neuropsychological tests selected to measure central areas of EF, and screened on clinical and demographic variables. Within the depressed group, a total of 56% were defined as EF unimpaired. These patients were characterised by higher intellectual abilities and fewer depression episodes than the subgroup of patients with EF impairment. The subgroups were similar in age at debut of illness, severity of depression, general psychopathology and global level of functioning. In conclusion, about half of patients with recurrent major depression have normal EF. Since cognitive impairment and depressive symptomatology seem to be distinct dimensions, a neuropsychological investigation could help to ensure optimal treatment in patients with recurrent major depression.

Key words: Major depression, non-psychotic, recurrent, neuropsychological tests, executive functions

Introduction

Major depression is a serious condition with a lifetime prevalence of 17% (Angst 1999). The majority of patients experience recurrence of episodes after recovery (Mueller 1999), and the risk of psychosocial impairment is high (Angst 1999).

It is commonly accepted that higher-order cognitive functions, the so-called executive functions (EF), are impaired in major depression on a group basis (Degl'Innocenti et al. 1998; Elliott 1998; Fossati et al. 1999; Merriam et al. 1999; Grant et al. 2001; Stordal et al. 2004). EF can be defined as a set of processes involved in complex intentional behaviour that 'control, integrate, organise and maintain other cognitive processes' (Pohjasvaara et

al. 2002). The concept can further be divided into several subcomponents (Lezak 1995), i.e. Pennington and Ozonoff's (1996) subdivision into verbal fluency, planning, working memory, inhibition, set-shifting and set-maintenance. These subcomponents can be operationalized by specific neuropsychological tests. The EF impairment as well as the depressive symptoms have been associated with dysfunction of frontal-subcortical systems (Mega and Cummings 1994; Goodwin 1997; Elliott 1998; Royall 1999; Mazziotta et al. 2000).

EF impairment has been suggested to be an early sign of cognitive impairment in patients with major depression (Austin 2001). The EF domain also seems impaired in drug-free patients (Porter et al. 2003). It has also been shown that EF are affected in

depressed patients who are in the remission or recovery phase of the disorder (Elliott 1998; Reischies and Neu 2000; Grant et al. 2001). The level of EF dysfunction in depressed patients is, however, disputed. Some studies have indicated that major depressed patients perform at the same level as controls on cognitive tests (Grant et al. 2001), whereas other studies have compared their performance to that of patients with traumatic brain-damage (Veiel 1997). In a recent study, patients with recurrent major depression performed significantly below that of healthy controls on tests of EF, but the severity of the impairment on a group basis was shown to be within the range of -0.15 to -0.89 standard deviations (S.D.) below the mean of the control group (Stordal et al. 2004).

There is, however, a general agreement that EF are essential for complex activities of daily living (Grigsby et al. 1998). A recent report from a study of patients with unipolar depression indicated that EF impairment predicted non-response to fluoxetine, and it was suggested that EF assessment in depressed patients could 'play a particular role in the pretreatment identification of subjects likely to respond to specific medications' (Dunkin et al. 2000). It is also possible that unimpaired EF can be a positive prognostic factor in patients with major depression, as suggested for patients with schizophrenia (Palmer et al. 1998). Thus, one should expect that depressed patients with normal EF will benefit more from pharmacotherapy and will have better everyday functioning than their EF impaired counterparts. From a clinical point of view, it is therefore of interest to know more about the frequency of depressed patients with normal EF and their clinical characteristics. In general, there is a lack of studies that identify depressed patients who are neuropsychologically normal, and in particular studies identifying EF unimpaired depressed patients.

In order to identify unimpaired patients, a careful selection of EF measures and a cut-off value to define EF unimpairment is needed. There is no generally accepted cut-off point for defining unimpairment or impairment in depressed patients. Heinrichs (2001) refers to -2.0 S.D. as the most often used cut-off value for neuropsychological impairment, whereas -1.5 S.D. was used as cut-off point defining EF impairment in a group of post-stroke depressed patients (Pohjasvaara et al. 2002). Palmer et al. (1997) used a combination of both neuropsychological test summary scores and neuropsychologist expert ratings in their evaluation of neuropsychological impairment in schizophrenic patients, while Newman et al. (2001) underscored the need to be impaired on more than one functional

measure to be defined as impaired. Thus, the question of impairment seems to be relative.

In the present study, a group of patients with recurrent major depression and a healthy control group were included and assessed on a set of tests measuring different subcomponents of EF. Impairment was defined from the distribution in the control group. The aim was to explore group differences between depressed patients and controls in EF. Then we estimated the prevalence of depressed patients without EF impairment and their clinical characteristics. We also wanted to explore whether EF was equally affected by age, level of education, sex and intellectual abilities in depressed and non-depressed subjects.

Material and methods

Subjects and clinical assessment

Forty-three depressed patients (age range 19–51 years) were included in the present study. The subjects have previously been described elsewhere (Egeland et al. 2003a,b; Stordal et al. 2004), but in this study two of the original patients were excluded because of missing data on one of the neuropsychological EF tests. The patients were examined at five different psychiatric hospitals in Bergen and Oslo, Norway. They were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I version 2.0) (First et al. 1995), and all subjects met DSM-IV diagnostic criteria for major depressive disorder, recurrent type without psychotic features (American Psychiatric Association 1994). The age at onset of depression ranged from age 7 to age 44, and the number of depression episodes from two to five ($n=26$ due to missing data). The patients were moderately to severely depressed, scoring a minimum of 18 points at the Hamilton Depression Rating Scale, 17 items (HDRS) (Hamilton 1960) and 21 points at the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979). The daily psychological, social and occupational functioning of the depressed patients was assessed with the Global Assessment of Functioning scale (GAF) from SCID (First et al. 1995). An indication of the general psychopathology of the patients was given by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962). At the time of cognitive testing, three of the depressed patients were unmedicated and information regarding medication was missing for two. Thirty-four patients were on antidepressants (SSRI, mianserin, nefazodone, venlafaxine or moclobemide), and none were on tricyclic antidepressant medication. As additional medication, 17

patients were on benzodiazepines and eight on antipsychotic medication (as a hypnotic). A healthy control group ($n=50$) was recruited from the local communities. The two groups were matched on age, gender, level of education and intellectual abilities as assessed by the Similarities test from the Revised Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler 1981). There were significant group differences for the Picture Completion test (Wechsler 1981) (Table I). The study was approved by the Regional Committee for Medical Ethics. All participants provided written informed consent to participate in the study.

Neuropsychological assessment and operationalization of EF

The neuropsychological assessment was performed within 3 days after the clinical psychiatric assessment. Each participant completed a set of neuropsychological tests, selected to assess central areas of executive functioning and intellectual abilities. A prior report showed that only some of the included EF tests separated depressed patients from non-depressed controls after adjusting for additional medication (benzodiazepines and antipsychotics) and psychomotor retardation (Stordal et al. 2004). These tests were the Paced Auditory Serial Addition Test (PASAT), the Digit Backward subtest (DB) from WAIS-R, the Controlled Oral Word Association Test (COWAT), the Failure to Maintain Set variable from Wisconsin Card Sorting Test (WCST) and the Colour-Word subtask from the Stoop Colour Word Test (Stoop). These five tests were used as measures of four different subcomponents or areas of EF. The PASAT measure (the sum of the 3- and 2-second interstimulus interval subtests) and the DB measure were used to assess working memory. The sum of words from the four COWAT subtests was used as a measure of verbal fluency. The WCST score was used as a set-maintenance measure and the Stoop variable as a measure of inhibition (Table I).

EF summary score

For the depressed group, the results from the four measures were normalised. Standardised scores were then calculated for the set-maintenance, inhibition, verbal fluency and working memory measure results. A Cronbach's coefficient alpha of 0.701 was found for the z -scores calculated from the four EF measures. The results from these scores were then summarised to obtain a continuous EF summary score.

Table I. EF and intellectual abilities tests and test results for the depressed group ($n=43$) and the control group ($n=50$).

	Assessment	Score	Control group M (SD), range	Depressed group M (SD), range	Choen's d	T -test sign.
Executive function tests						
PASAT (Gronwall 1977)	Working memory	Number of correct summations from the sum of 3- and 2-sec interstimulus intervals	95.40 (16.58), 45–120	79.21 (24.28), 24–118	0.78	0.000
DB (Wechsler 1981)	Working memory	Number of correct repeated sequences	6.90 (2.25), 3–13	5.81 (1.67), 3–11	0.55	0.001
COWAT (Benton and Hamsher 1989)	Verbal fluency	Total score of four components: letter F, letter A, animals and clothes	77.27 (15.42), 47–111	64.26 (15.68), 28–93	0.84	0.000
WCST (Heaton et al. 1993)	Set-maintenance	Number of failures to maintain set	0.73 (1.27), 0–6	1.49 (1.65), 0–6	0.52	0.007
Stoop (Mitrushina et al. 1999; Stroop 1935)	Inhibition	Response time (sec) reading aloud incongruent colours (colour-word)	43.72 (9.56), 24–68	54.37 (12.97), 33–85	0.93	0.000
Intellectual abilities tests						
Similarities (Wechsler 1981)	Verbal abilities, abstraction	Number of correct answers	21.14 (4.31), 2–28	19.91 (5.52), 4–27	0.25	0.232
Picture completion (Wechsler 1981)	Visual analyse, concentration	Number of correct answers	15.92 (2.22), 10–19	14.69 (3.09), 6–19	0.46	0.029

Definition of EF unimpairment

Because low performance in one cognitive domain is frequent among normal subjects (i.e. Heaton et al. 1991), impaired performance in several EF measures should be required to define EF impairment. The exact number of areas was defined from the distribution in the control group (Table II) which show that the majority of controls was impaired in zero or one areas. EF unimpairment was defined from the distribution of EF scores in the control group (Table II). We considered 84% of the controls to be unimpaired as a reasonable number. Thus, we defined the cut-off point for EF impairment as performance equal to or below -1.0 S.D. in the control group on more than one area of EF (see Table II) and accordingly unimpairment as performance above -1.0 S.D. (a good definition of impairment should probably identify a smaller proportion of the population). To be defined as impaired on working memory, both the PASAT and the DB scores had to be impaired.

Data analysis

The SPSS for Windows 11.0 was used for statistical analyses. Skewed distributions were handled using power-transformation (the Stroop measure) or dichotomization (the WCST variable) and standardised scores (z -scores) were calculated using standardised procedures in SPSS. Choen's d was used as a measure of effect-size (Rosnow et al. 2000). To explore associations between demographic/clinical characteristics and EF impairment, linear and categorical analyses were performed using Pearson correlation and Student t -test/Pearson Chi-square test, respectively. A multivariate regression model was used to explore the interaction between demographics/intellectual abilities and diagnosis (dichotomous variable indicating depression or non-depression) in the prediction of EF impairment. In this model, the EF summary score was treated as dependent variable (i.e. level of EF impairment = diagnosis + age + age \times diagnosis). Demographic and intellectual abilities variables were dichotomised according to the median value for all subjects and used as independent variables. All statistical tests were two-tailed with an α level of 0.05.

Results

There were large and statistically significant group differences between depressed patients and controls on all selected EF measures (Table I).

Clinical and demographic characteristics of the seven best and the seven worst performing individuals in EF are shown in Table III. Among the seven patients performing below -1.0 S.D. in EF, all were on antidepressants, none were on antipsychotic medication and only one was on sedatives (benzodiazepines). Of the seven patients performing above 1.0 S.D., one was on antipsychotic medication, four were on sedatives and two were unmedicated with regard to antidepressant medication.

According to the definition of EF unimpairment, 56% of the depressed patients were defined as EF unimpaired (Table II). EF unimpairment was present in both depressed patients and controls, but there was significantly more EF unimpairment in the control group than in the depressed group. Sixteen percent of the controls were EF impaired. Thus, although statistically significant, there were EF impaired subjects in the control group and patients without EF impairment in the depressed group. An odds ratio of 4.2 (95% C.I., from 1.6–10.9) indicated that the odds of EF impairment was approximately four times higher in the depressed group than in the control group. An explained variance of 10% was found. In other words, 90% of the variance in EF could be explained by other factors. Thirty-five percent of the depressed patients had zero impaired EF areas as compared to 54% of the controls. The four different EF areas did not discriminate equally between depressed patients and controls (Table IV). The greatest difference was seen for verbal fluency followed by inhibition, set-maintenance and working memory.

In the linear analyses, no statistically significant correlations were found between the EF summary score and the following clinical variables: in/out patient, age at onset, number of episodes, severity of depression, level of general psychopathology and global level of functioning (Table V). The mean age in the control group was 32.9 years compared to 35.2 years in the depressed group. The mean level of education in years for the control group was 13.9

Table II. Percentage of depressed group ($n=43$) and control group ($n=50$) that perform equal to or below cut-off point on from zero to four of the EF areas, and total percentage of each group that are without and with EF impairment.

	0 areas (%)	1 area (%)	2 areas (%)	3 areas (%)	4 areas (%)	Without imp n (%)	With imp n (%)	Total n (%)
Depressed group	34.9	20.9	23.2	14.0	7.0	24 (55.8)	19 (44.2)	43 (100)
Control group	54.2	33.3	8.3	2.1	2.1	42 (84)	8 (16)	50 (100)

Chi-square test, $P < 0.001$

Table III. Clinical and demographic characteristics of the seven worst (< -1.0 S.D.) and seven best (> 1.0 S.D.) performing individuals in EF.

EF summary z -score	Age group	Sex	Education	In/Out patient	GAF	BPRS-E total	HDRS total	MADRS total
-1.75	30	M	15	In	40	41	26	31
-1.74	30	F	17	Out	65	38	19	28
-1.55	20	M	18	Out	40	42	27	31
-1.46	30	F	18	Out	50	47	22	36
-1.26	30	M	13	In	35	43	21	36
-1.20	20	F	10	In	50	52	26	30
-1.08	50	F	18	Out	50	47	26	31
1.07	40	F	15	In	45	50	27	35
1.18	40	F	12	Out	45	42	27	25
1.21	30	M	17	Out	55	46	20	24
1.26	30	F	12	Out	45	36	18	26
1.45	30	M	13	In	55	42	21	23
2.00	20	F	11	In	45	51	23	31
2.15	40	M	9	In	45	43	23	31

compared to 13.8 for the depressed group. As for the measures of intellectual abilities, controls had a mean scaled score of 10.5 on the Picture Completion test and 11.6 on the Similarities test from WAIS-R, whereas depressed subjects had 9.8 and 10.9, respectively. There were statistically significant correlations between level of EF and age (Pearson correlation = 0.349, $P=0.022$), education (Pearson correlation = -0.425, $P=0.005$), and intellectual abilities as measures with the Picture completion (Pearson correlation = -0.557, $P<0.001$) and the Similarities (Pearson correlation = -0.690, $P<0.001$) subtasks.

In the categorical approach, a statistically significant group difference between the EF unimpaired and impaired subgroups for the number of episodes variable was found, with a lower number of depression episodes in the non-impaired group. There were no statistically significant differences between the groups regarding the following clinical variables: in/out patient, age at debut, severity of depression, level of general psychopathology and global level of functioning. The results from the categorical approach were therefore similar to the result from the linear approach. The mean age in the control group without EF impairment was 33.4 years compared to 33 years in the depressed group. The mean age in

the control group with EF impairment was 30.3 years compared to 37.9 years in the depressed group. As for the measures of intellectual abilities, controls without EF impairment had a mean scaled score of 10.6 on the Picture Completion test and 11.4 on the Similarities test from WAIS-R, whereas depressed subjects had scores of 10.3 and 11.9, respectively. In the EF impaired subgroups, controls showed a mean scaled score of 9.9 on the Picture Completion test and 12.6 on the Similarities test compared to 9.2 and 9.7 for the depressed subgroup. A statistically significant group difference was found for intellectual abilities as measured with the Similarities test ($t=2.535$, $P<0.015$), but not for age ($t=-1.948$, $P<0.058$) and education ($t=1.719$, $P<0.093$), although these variables almost reached significant levels. The depressed patients without EF impairment were thus characterised by fewer depression episodes and higher intellectual abilities than patients with EF impairment, but the groups were similar on measures of symptomatology, general psychopathology and global functioning.

For the interaction between age and diagnosis in prediction of level of EF performance (the EF summary score) a β value of 0.286 was found ($P<0.093$) in the linear regression model. In other words, subjects both being depressed and older than

Table IV. Distribution of depressed group ($n=43$) and control group ($n=50$) in the four EF areas: inhibition, set-maintenance, verbal fluency and working memory.

	Depressed patients		Controls	
	Equal to/below cut-off point (%)	Above cut-off point (%)	Equal to/below cut-off point (%)	Above cut-off point (%)
Inhibition	39.5	60.5	16	84
Set-maintenance	41.9	58.1	22.4	77.6
Verbal fluency	44.2	55.8	16.3	83.7
Working memory	11.6	88.8	8	92

Table V. Clinical variables and EF impairment in the depressed group ($n = 43$), and subgroups without ($n = 24$) and with ($n = 19$) EF impairment.

	Depressed M (SD)	Pearson Correlation ^a	Without imp M (SD)	With imp M (SD)	Sign. 2-tailed
In:Out patients (%)	61.9:38.1	-0.090	61:39	63:37	0.879 ^c
Age at debut (years)	23.6 (9.5)	0.225	21.5 (7.9)	26.2 (11.0)	0.116 ^d
Number of episodes ^b	3.8 (2.9)	0.184	2.8 (0.9)	3.8 (1.2)	0.017 ^d
HDRS total	22.5 (4.5)	-0.095	22.2 (3.7)	22.8 (5.4)	0.687 ^d
MADRS total	28.8 (4.5)	-0.083	28.8 (4.9)	28.8 (4.1)	0.975 ^d
BPRS-E total	43.2 (6.6)	0.146	43.0 (8.1)	43.3 (4.2)	0.894 ^d
GAF	46.7 (8.8)	0.008	46.7 (10.6)	46.7 (6.0)	0.995 ^d

^a Significant correlations are marked with ‘*’.

^b $n = 26$: non-impaired subgroup ($n = 14$), impaired subgroup ($n = 12$)

^c Chi-square test.

^d Student t -test.

the median value were more likely to be EF impaired. There were no significant interactions between diagnosis and education, sex, or intellectual abilities as measured with either the Picture Completion test or the Similarities test from WAIS-R.

Discussion

In the present study a significant and large group difference between depressed patients and controls was found for all selected EF measures. This finding is in line with previous studies (i.e. Degl’Innocenti et al. 1999; Austin et al. 2001; Stordal et al. 2004). However, the study points to the fact that still a significant proportion of patients with recurrent major depression show unimpaired EF when moderately to severely depressed. Furthermore, patients without EF impairment according to our definition were similar to patients with EF impairment regarding clinical variables such as severity of depression, general psychopathology and global functioning, but they were characterised by fewer depression episodes and higher intellectual abilities than patients with impairment.

The definition of unimpairment chosen in this paper can be disputed. The number of impaired patients in the present study is higher than that reported in a study by Reischies and Neu (2000). They found that about a third of depressed patients were impaired on measures of fluency and memory, but they used the fifth percentile as cut-off point. EF impairment in groups of patients with major depression is frequently reported in the literature (i.e. Degl’Innocenti et al. 1998; Fossati et al. 1999; Stordal et al. 2004), although some studies have not found EF impairment or only modest evidence of such (Purcell et al. 1997; Grant et al. 2001). The association between major depression and EF impairment, which seems to be a strong association due to the tendency of mostly positive findings in the

literature, can therefore put an extra ‘illness burden’ to an already severely ill group of patients. To the best of our knowledge, the present study is the first to focus on the recurrent major depressed patients with unimpaired EF, although similar studies have been performed on other depressed patient samples, schizophrenic patients as well as patient groups with neurological diseases (Palmer et al. 1997; Reischies and Neu 2000; Pohjasvaara et al. 2002). It has shown that, although major depressed patients show EF impairment on a group basis (Stordal et al. 2004), this study has shown that not all patients within the group are EF impaired. The present study shows that the association between major depression and EF impairment is rather weak. Not only are many patients unimpaired on EF tests, but most of the variance in EF could be explained by other factors than the depression itself. These findings underscore that there is large heterogeneity within the groups of recurrent major depressed patients with respect to EF impairment.

Because one main hypothesis is that each repeated depression episode ‘leaves a mark’ in the brain (Sheline 2000), only patients with recurrent major depression were included in the study. Although the depressed patients with EF impairment in the present study had more depression episodes than the patients without such an impairment, other studies have not found such an association (Reischies and Neu 2000). The present study has also demonstrated that the EF impairment found in major depressed patients does not seem to be associated with clinical variables as severity of depression, general psychopathology and functioning, although this could be expected from a clinical point of view. Also this finding is in agreement with some of the prior studies (i.e. Degl’Innocenti et al. 1998), but not others (i.e. Grant et al. 2001). In fact, it is striking how inconsistent the results in the literature are when correlating clinical variables to

cognitive performance. This inconsistency may in part be explained by a large percentage of patients being neuropsychologically normal. Furthermore, a longitudinal study by Rieschies and Neu (2000) showed that patients with cognitive impairment were still impaired when recovered from their depression. The cognitive impairment and the depressive symptomatology therefore seem to be distinct dimensions.

There was a tendency towards age playing a larger role for EF performance in depressed patients than in control subjects. It is an established fact that with increasing age there is a decline in cognitive functions. However, in schizophrenic patients, a larger age-related decline was found in EF (abstraction) compared to other cognitive functions (Fucetola et al. 2000). Thus, it is possible that recurrent depression per se may accelerate the natural ageing processes of the brain. But this does not explain why only a small subgroup of the recurrent depressed patients was EF impaired. Another explanation is that the EF impaired subgroup can be more at risk for the development of dementia, although O'Brien et al. (2001) found no relation between cognitive impairment in depression and dementia in a neuropathological study. The relation between depression and age in prediction of EF impairment should be explored in further studies.

The strengths of the present study include use of a well-defined depression sample, well-matched controls and several neuropsychological tests assessing different aspects of EF. However, there are several limitations to the study. Firstly, the patients included in the present study were on antidepressant drugs when neuropsychologically tested. There is a possibility that in an unmedicated sample, the percentage of EF impaired depressed patients would be higher. Secondly, the patients were also rather homogeneous with respect to symptoms of depression due to the specified inclusion criteria. The association between level of performance on tests of executive function and clinical symptomatology should thus be examined in a more heterogeneous sample of depressed patients. Third, the selection of EF variables is critical. The failure to maintain a set variable from the WCST is a somewhat problematic and complex measure and may not be the best variable to operationalise EF. Still, this measure was the only WCST variable that separated depressed patients from healthy controls in a former study (Stordal et al. 2004), and it has been used in earlier studies of depressed patients as an EF variable (Degl'Innocenti et al. 1998; Grant et al. 2001). And, finally, since there is no generally accepted standard for defining EF impairment in depressed patients, our choice of cut-off point may be criticised.

In conclusion, our results with regard to group differences between depressed and non-depressed subjects in EF are in accordance with previous studies. Despite this large group difference, we found that 56% of depressed patients still are unimpaired in EF when unimpairment is defined from the distribution in the control group. A recent report showed that major depressed patients with EF impairment were non-responders to fluoxetine (Dunkin et al. 1999). It is therefore possible that patients with EF impairment to a lesser extent benefit from pharmacotherapy, and probably also from psychotherapy compared to patients with normal EF. A recent report showed problem-solving therapy to be more effective than supportive therapy in reducing depressive symptoms and disability in elderly patients with major depression and EF dysfunction (Alexopoulos et al. 2003). Since cognitive impairment and clinical symptomatology seem to be distinct dimensions in recurrent major depression, a neuropsychological investigation may be included to identify patients with special treatment needs in order to ensure optimal treatment. In future studies one should thus be aware of the heterogeneity of recurrent depressed patients with respect to cognitive impairment, and explore the association between major depression and cognitive impairment in longitudinal studies.

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VIEWPOINT

Problems associated with the classification and diagnosis of psychiatric disorders

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Abstract

Several methodological issues of classification of psychiatric disorders are addressed. Beside some historical aspects and basic characteristics of the classification of mental disorders, the advantages and disadvantages of the syndromatological and nosological classifications are broadly described. Finally the current situation of the international standardisation of psychiatric classification and particularly the improvement of reliability by using operationalised procedures is discussed.

Key words: Classification of psychiatric disorders, nosology, syndromes, polydiagnostics

Introduction

Like every branch of science, psychiatry attempts to give a name to the phenomena of its area of research and to classify them according to various aspects, in order to allow systematic investigation of the phenomena, and the communication and comparison of the results of observations. The specialised terms used in this process, abbreviations for more or less complex facts, should be defined as accurately as possible to guarantee optimal scientific communication (Möller 1976).

Classification means two things:

- a. Primarily the subdivision of diversity (various characteristics, populations of cases) into a system ordered according to classes (classification). The term “classes” describes an entirety of elements with common characteristics.
- b. Secondly, the assignment of individual characteristics or cases to the classes of such a system (diagnosis).

Five hundred years ago, Kraepelin founded the first systematic classification of all psychiatric disorders.

His systemisation was based on phenomenological descriptions given by famous clinicians of the nineteenth century. Various authors later made different modifications to Kraepelin’s classification. Some composed additional subclasses, others questioned the subclassification described by Kraepelin or redefined the interrelationship between symptoms and diagnostic classes. Finally international efforts led to the modern operational classification systems.

The classification of psychiatric disorders has been criticised generally for various reasons and from different sides. The idiographic approach is mainly dedicated to an individual view of each patient as unique in his development, personality and pathogenic situation (Meyer 1907; Menninger 1963). It questions whether it is at all possible for a classificatory assignment to do justice to a patient’s individuality. In contrast, however, such an approach does not exclude one in which an individual case is classified as belonging to a class of cases with similar characteristics and patterns, it only meaningfully complements it and thus makes specified medical interventions available to the individual case (von Zerssen 1973a,c). The classification of psychiatric

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disorders is even more radically criticised by authors of the so-called "anti-psychiatry". They suggest to refrain from any classification of psychiatric disorders as a harmful "labelling" of the patient (Laing 1972; Foudraine 1973; Scheff 1973; Szasz 1973). This position appears untenable, at least in its radical form in which the difficulties in the lives of mentally ill patients, e.g., schizophrenics, simply result from the diagnostic labelling of their behavioural disorders and from other people's attitudes which are influenced by this label (Schipkowensky 1974; von Zerksen and Koeller 1976; van Praag 1978; Bean 1979).

Another counter-argument to such more or less critical attitudes towards a classification of psychiatric disorders is that it is the classification of psychiatric disorders itself that creates the basis for research of the associations in the multifactorial development of such disorders. Furthermore, knowledge about these conditional associations is a prerequisite for rational and empirically well-founded treatment of these disorders. The classification of mental disorders therefore does have advantages. This can be demonstrated with a simple example. If there were no classification into non-organic and organic psychoses there could definitely be no differentiation made in the treatment of these two disorders. Organic psychoses might then be treated only with neuroleptics and additional psychosocial procedures, instead of treating the somatic cause of the organic psychosis. In such a case it would have lethal consequences for the patient if one did without adequate classification and diagnosis. A further example is the classificatory differentiation between schizophrenic psychoses and depressions. Only the differentiation between the two allows the specific psychopharmacological treatment of both illnesses with the treatment that has proved effective: while neuroleptics are indicated in schizophrenic psychoses, antidepressants should be used to treat depression. The lack of diagnostic differentiation would prevent the types of treatment that are nowadays known to be optimal for each disorder group being applied according to the respective indication.

In the early stages of behavioural therapy hardly any attention was paid to the classification of mental disorders. According to the learn-theoretical concepts, disorders of behaviour were broken down into single elements (symptoms), whose stimulus/reaction relationship was clarified through an individual behavioural analysis and then modified on this basis with behavioural therapy methods. The classification of mental disorders, as developed in psychiatry, was only taken into account as the amount of experience increased, i.e., it was recognised that at least the rough classification, as described above, is of great

relevance for the therapeutic approach chosen, and its efficacy, and that the field in which behavioural therapy is applied primarily covers psychologically explainable disorders. Based on their own theoretical ideas, and limited from the start to neurotic disorders, the psychoanalytical schools developed their own systems to classify symptom neuroses and character neuroses, some of which were later integrated into psychiatric classifications, like anxiety neuroses or obsessive compulsive neurosis.

Besides the more or less total rejection of the classification of mental disorders, there are the methodologically orientated critics who, although they do acknowledge the essential justification and even necessity of classificatory systematics of mental disorders, take offence at shortcomings of the respective, commonly used systems of classification (Costello 1970; Akiskal and Webb 1978; Kendell 1978, 1981; Roth 1978; Spitzer and Klein 1978; Goodwin and Guze 1979; Möller and von Zerksen 1984). In their view the classification of mental disorders should be continuously adapted according to the results of empirical research in order to ensure the validity of the classification and the reliability of the diagnostics. The recognition of problems with the classification of mental disorders and the search for ways to improve them thus remains a central concern of research.

The following paper will describe neither the historic development of various attempts to classify mental disorders (see Zilboorg 1941; de Boer 1954; Ackerknecht 1957; Leibbrand and Wettley 1968) nor the individual nosological systems that were based on various regional traditions (see Meyer 1961). Instead, some principal problems in the classification of mental disorders and current attempts to solve them will be outlined.

Basic problems in the classification of mental disorders

Logical classifications are characterised by precise stipulation of the characteristics or combinations of characteristics that define the individual classes, whereby the reasons for classification are retained (the criterion according to which the classification was made), all phenomena that occur in the area of evaluation are considered, and inclusion and exclusion criteria for assignment of individual cases to classes are defined. Most empirical classifications do not achieve the criteria valid for logical classifications (Mombour 1975, 1976; Kendell 1978). This is related on the one hand to the complexity of phenomena in real patients, which can only be assigned to classes by different kinds of abstractions, and on the other hand to the fact that empirical

classification normally attempts to form classes not only based on external characteristics, but also to use postulated or proved conformances as characteristics for classification and thus to create a “natural” system as opposed to an “artificial” system.

If one considers the complexity of the appearance of mental disorders, the continuity between the various types and the insufficient knowledge about the way they originated, most of what has been said about the difficulties associated with the classification of mental disorders becomes understandable. This is particularly true for attempts at classification in which not only the temporal cross-section of symptoms, but also assumptions about causal factors, the spontaneous course and the response to certain therapeutic procedures serve as criteria for classification (von Zerssen 1973e). However, it is precisely these theoretical factors that are of great relevance for the classification of mental disorders, as for all classifications (Baumann 1987).

Numerous classification criteria and, therefore, varying classifications are readily conceivable: e.g., aetiopathogenesis, phenotype, course, therapeutic response, etc. Different classifications result, depending on the criteria chosen (e.g., Kraepelin’s nosological system or that of the Kleist–Leonhard school), sometimes with different levels of abstraction (syndromatology, nosology). The classes thus formed represent the result of an idealising abstraction and selection process. They do not correspond with entities that really exist, but are theoretical terms or constructs (Möller 1976) and therefore depend on the respective theoretical position.

This point of view, together with the fact that there are smooth transitions between the various classes, comes closest to doing justice to the interpretation that the classification of mental disorders is basically a typology (von Zerssen 1973b–e). “Types” include all characteristics on which the similarities between the objects belonging to them depend, even if some or even most of these objects do not show every characteristic that constitutes the type. Types do not really exist, but arise through abstraction of real facts. They represent a sort of “original form” around which the real objects vary in the configuration of their individual characteristics. Due to their own blurred definition, conceptions of types have a broader field of application than conceptions of classes. This is because they also do justice to ranges of objects in which unclear borders between different phenomena make a clear separation into individual classes more difficult or even impossible. Under this aspect typological classifications of mental disorders appear to be more suitable than categorial classification. One can differentiate between “extreme” and “accumulation” types. Ex-

treme types are the extremes of normal series of variations, e.g., mental retardation as an extreme variation of the normal distribution of intelligence. Accumulation types are centres of accumulation of variable forms of pathological behaviour patterns, such as the subtypes of schizophrenia or the different exogenous reaction types (acute exogenous psychoses), for example.

Besides classification into classes or types, as is characteristic particularly for the nosological classifications of psychiatry, it is possible to classify mental disorders on a dimensional basis (Eysenck 1960, 1970; Katz et al. 1966). In the most simple case such a system is one-dimensional, in that it simply contains a continuum from optimal psychosocial adaptation through to the most severe degrees of psychosocial disintegration (Goldberg et al. 1970; Foulds and Bedford 1975). On the other hand, multidimensional systems are mostly based on concepts of variations of several character traits or behavioural patterns. Eysenck in particular (1970) propagated the dimensional classification of mental disorders, based on behavioural theoretical conceptions and the results of multivariate statistical analyses of questionnaires on personality traits. In this case the phenomena are arranged in a continuum that is characterised by certain dimensions – Eysenck proposed neuroticism, psychoticism and introversion/extroversion. Eysenck’s basic assumption that dimensional rather than classificatory systematics apply to the real conditions, since there is no basic difference between the characteristics of healthy and pathological behaviour, is not undisputed (Kendell 1978). This conception may apply to personality disorders and oligophrenias, but at least for the psychoses one can expect deviations from the norm in which on the one hand qualitatively novel elements beyond the normal range of events occur (e.g., hallucinatory perceptions) and on the other hand an abnormal combination of normal characteristics (von Zerssen 1973e).

Independent of the question whether dimensional, categorial or typological classification of mental disorders better corresponds to the real situation, any dimensional systematics become categorial or typological if certain degrees of expression of certain behavioural patterns are rated as “mentally healthy” or “mentally ill”, or as diagnostically, therapeutically or prognostically relevant, on the basis of statistical averages. The main types of psychopathological phenomena are then rated as extremes (extreme types) of certain characteristic traits or behavioural patterns. In Eysenck’s systematics, which attempts to portray the main types of psychopathological phenomena as extreme variations of normal personality traits, hysteria is characterised as a combination

of extreme neurotic tendencies with extraversion, for example, and schizophrenia as a combination of extreme psychoticism with neurotic tendencies and introversion.

In order for a classification of mental disorders to serve as a useful basis for decisions and interventions, at least the following criteria must be fulfilled:

- a. the classification must enable optimal prognoses about the spontaneous course and therapeutic response to be made;
- b. it must enable conclusions to be drawn about possible causal factors;
- c. it must enable individual cases to be assigned reliably to classes or types.

The better a classification of mental disorders fulfils these criteria, the better is it suited to everyday clinical practice (Möller et al. 1978).

Syndromatological classification

Syndromatological classification is seen as an alternative or addition to nosological classification. This is related among other things to the validity and reliability problems of nosological psychiatric classification, which are viewed very critically by some authors (see Costello 1970), and also in particular to the development of psychopharmacology, which in the opinion of many of its advocates is orientated rather towards syndromes than nosology (see Möller 1987).

The syndromatology of mental disorders arose on the basis of clinical intuition. It describes the joint appearance of symptoms without considering the conditions of their origins. Psychopathological syndromes are unspecific with respect to the aetiopathogenetic factors on which they are based: the same syndromes may have different causes, and the same causes can result in different syndromes (see von Zerssen 1973d). However, there are certain global associations, for example that psychoses with a somatic cause mostly appear as acute exogenous reactions types or chronic organic brain syndrome.

Statistical methods to investigate the accumulated joint occurrence of single symptoms are the factor and cluster analyses. The data on which evaluations performed with these methods of multivariate statistics are based are obtained from psychopathological findings recorded with rating scales (Möller and von Zerssen 1982, 1983). When taken together, such evaluations, performed with different rating scales in different patient samples and countries, resulted time and again in similar group factors or symptom clusters, and the assignment of the symptoms to syndromes proved to be relatively stable (see

Mombour 1972; Overall and Klett 1972; Lorr 1974; Cairns et al. 1982; Baumann and Stieglitz 1983; Möller and Hacker 1988). The syndromes ascertained with multivariate statistical methods correspond to some of the traditional syndromes that arose on the basis of clinical intuition: e.g., paranoid-hallucinatory syndrome, manic syndrome, depressive syndrome, apathetic syndrome, hypochondriac syndrome, phobic-anancastic syndrome, mnemonic syndrome (Mombour 1974). These syndromes can therefore be seen as empirically confirmed, if one assumes that the term "clinical syndrome" also means the accumulated joint occurrence of single symptoms. Inclusion of a larger variety of psychopathological states, in particular those with a somatic cause or of the neurotic kind (Meyer 1972), would probably confirm further clinically described symptoms. The factor emotional instability (described by Eysenck (1970) and other authors as "neuroticism") seems to be relevant for neurotic disorders since it obviously differentiates between healthy subjects and neurotics (Fahrenberg et al. 1978).

Syndromatological classification of cases can be achieved on the basis of multivariate statistical analyses of patient samples by combining several syndromes, each of a certain degree of expression, to typical syndrome profiles. Such syndrome profiles allow one to form diagnostic groups, under consideration of the similarity of the profiles and without considering the clinical diagnosis. This was demonstrated by Lorr (1966), using endogenous psychoses as an example. These typical syndrome profiles may correspond to known diagnoses. However, if this is not the case, it usually remains unclear what should be done with the newly found diagnostic types. Earlier attempts to form a new kind of classification with such cases have not yet been realised on a larger scale (Mombour 1976). Instead, the opposite path was followed, i.e., average profiles for each diagnosis group were empirically ascertained on the basis of clinical diagnoses (Mombour 1974; Möller and von Zerssen 1980; Baumann and Stieglitz 1983; Gebhardt et al. 1981). In principle, this procedure can also be applied at the symptom level, although a frequency analysis is normally performed here (Mombour 1974; Diebold and Engel 1977; Pietzcker et al. 1981). The utilisation of average profiles facilitates the psychopathological comparison and syndromatological or nosological assignment of patient groups as well as the course analysis of single case evaluations and group statistical evaluations and improves their information content (Mombour et al. 1973; Wing et al. 1974). Furthermore, syndromes give rise to new prognostic

possibilities (Wittenborn 1977; Möller et al. 1981; Möller and von Zerssen 1986).

A syndromatological classification with syndrome profiles on the basis of rating scales appears to be advantageous for various reasons: development of more precise algorithms, greater reliability, greater ability to differentiate through quantifying presentation of syndrome profiles. However, if it just related to symptom patterns, a syndromatological classification cannot completely replace a nosological classification since it does not consider aetiology, course and therapeutic response. Under this aspect the diagnosis of a syndrome is only rarely used as a final diagnosis but rather as a reliable step on the way to a nosological diagnosis.

In order to study the genesis of a syndrome, information has to be collected about the biography, primary personality, damaging noxious substances, etc. This approach led to the discovery of the “final common path”, that leads from the multiple conditioning factors to the uniform clinical syndrome (von Zerssen 1973d). If one also includes information about therapeutic response in such an analysis (Paykel 1977), the disadvantages of a syndromatological classification described above no longer apply and one obtains a new type of nosological systematics.

Nosological classification

In addition to symptoms, the nosological classification of mental disorders considers the course and response to therapeutic procedures and, if known, the aetiology and pathogenesis of the symptoms. Owing to the greater complexity which results from the inclusion of so many factors, particularly known and suspected aetiopathological factors, there are significantly more divergent attempts at classification than in the area of syndromatology (von Zerssen 1973c).

The new nosological classifications commonly used in psychiatry today are based to a great extent on the classification designed by Kraepelin, which was based on clinical intuition (Kraepelin 1910). Kraepelin was able to draw up “disorder units” and unite them in one system by considering simultaneously the overall cross-sectional and longitudinal clinical pictures and the degree to which they could be influenced therapeutically, together with the anatomical and aetiological pathological basis. Kraepelin categorised the main groups of disorders according to causal factors, most of which however were hypothetical, and some of which still are. Bonhoeffer’s discovery (1912) that different somatic causes can give rise to the same psychopathological symptoms, and that the same cause can give rise to

various psychopathological symptoms, was the basis for subsequent fundamental criticism of Kraepelin’s nosology. However, the basic features of his nosology still became accepted worldwide and are still accepted to this day. The non-specificity of mental disorders with respect to the causal factors was later interpreted as a result of interference by several aetiopathologically relevant factors (genetic disposition, primary personality, biography, poisons, etc.) (Jaspers 1965; Bleuler 1972). In this context one refers to the multiconditionality of mental disorders.

Not only was the basic conception of Kraepelin’s “disorder units” repeatedly questioned (see Kendell 1978), but there were also critics of its special nosological classification. The critics either favoured the extreme of a pooling of the generally differentiated types schizophrenia, manic-depressive disorder and schizoaffective disorder as an “Einheitspsychose” (Rennert 1977) or propagated the other extreme of their dissolution into numerous special forms according to genetics, symptoms and course (Leonhard 1968). However, twin and family studies, as well as studies of course, show that the concept of a uniform psychosis cannot be maintained since affective psychoses can be differentiated from schizophrenic psychoses with respect to genetic aspects and the course of the disorder (Angst and Scharfetter 1979; Tsuang and Dempsey 1979; Zerbin-Rüdin 1980; Cichon et al. 2001; Schumacher et al. 2002; Maier et al. 2003; Neumeister et al. 2004). With respect to further differentiation, these days the concept of schizoaffective psychoses (Brockington 1981) as a special type between schizophrenic and affective psychoses is generally accepted based on genetic and catamnestic findings (Angst et al. 1979; Tsuang and Dempsey 1979; Marneros et al. 1986). The differentiation between unipolar depression and bipolar (manic-depressive) psychoses can be seen as established on the basis of empirical findings (Angst and Perris 1968; Marneros et al. 2000).

Evaluations of the different responses of various disorders to certain types of treatment (Carney et al. 1965; Schou 1980; Möller 1987) appeared to justify the traditional syndromatology and partly also the psychiatric nosology – at least as far as the rough classification was concerned: e.g., lithium is only effective for prophylaxis in affective and schizoaffective psychoses; electroconvulsive therapy is very effective for endogenous but not for neurotic depression (dysthymia); neuroleptics mainly influence the symptoms of schizophrenic psychoses but not depression to a similar degree.

The application of statistical procedures, particularly of the multivariate kind, opens up new possibilities for the consolidation, extension and revision

of traditional nosological conceptions. Not only are data from psychopathological parameters used, but also anamnestic, somatological and other data. For example, Everitt et al. (1971) used cluster analyses to divide a population of psychiatric patients into four groups with the diagnoses mania, depressive phase of a manic-depressive psychosis, acute paranoid schizophrenia and chronic schizophrenia. Roth et al. (1974) used multivariate statistical analyses of the symptoms of patients with affective disorders to differentiate them into three symptom groups, which corresponded to the diagnoses endogenous depression, neurotic depression and anxiety neurosis. Paykel (1977) included in the multivariate statistical analysis of his patient sample not only data about symptomatology but also information about causal life events, premorbid personality and therapeutic response, and thus compiled a classification of the non-psychotic depressions into neurotic depression and non-psychotic chronic depressive reaction. On the basis of statistical analyses of the symptomatology in various patient samples, several authors investigated the frequency of occurrence of transitional forms between the nosological types (Carney et al. 1965; Kendell and Gourlay 1970). The results of these investigations were partially inconsistent. Nevertheless, altogether the indications for the validity of psychological nosology, at least in its rough definition, prevail.

International standardisation of psychiatric classification

Up to 1970, there were occasional but considerable discrepancies between the psychiatric nosology of different countries and even between that of different psychiatric schools within countries. The requirements for an international standardisation of psychiatric classification were fulfilled by the creation of an internationally accepted classification of mental disorders in the frame of the *International Classification of Diseases* (ICD), compiled by the World Health Organisation. Apart from modifications, the psychiatric part of the ICD is based on Kraepelin's nosological system. It is mainly structured according to aetiological and syndromatological aspects as well as according to characteristics of disorder course. While Kraepelin classified the main groups of disorders according to causal factors, the higher classification criterion of mental disorders in the ICD is syndromatological. Deficits in the categorisation (Mombour 1975, 1976) – such as a change of the classification principles – are a common feature of all currently available psychiatric classifications. They reflect the incomplete knowledge about mental disorders. In the case of the ICD

they are also accentuated by the necessary compromises of an international system. The 9th revision of the ICD, introduced in 1977 (World Health Organization (WHO) 1977), differs from the 8th revision particularly through the introduction of multiaxial or multicategorical diagnostics (Mombour 1980). In this system, a patient's diagnosis is simultaneously characterised by several numbers from the whole range of the ICD. Thus the first number from the chapter on psychiatric disorders in the ICD may stand for the clinical picture, the second from a different chapter for the underlying somatic illness.

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association (APA) 1980), was introduced by the American Psychiatric Association in 1980, and was partially conceived according to different classificatory criteria. Many of its definitions of various disorders no longer corresponded to the ICD-9 (compare, for example, the DSM-III and ICD-9 diagnoses of schizophrenia, Morey and Blashfield 1981). These changes were partially a consequence of the fact that certain "poor compromises" had to be made based on the desire for international standardisation. Furthermore, they were supposed to better represent the current level of empirical knowledge. In the DSM-III the individual diagnoses are defined by short clinical descriptions of the clinical picture and through operationalised diagnostic criteria (see below). In addition, in the DSM-III a so-called multi-axial classification with five axes was introduced, which was supposed to allow various areas of information relevant for prognosis and therapy to be recorded separately. The first axis serves to record the current psychopathological disorder (syndrome diagnosis), the second a personality disorder. On the third axis physical disorders relevant for the aetiology or treatment of the psychopathological disorders documented on the first two axes can be registered. On Axis 4 possible situation-related triggers (life events) of the current mental disorder can be evaluated according to their type and stress intensity. On Axis 5 the highest degree of social adaptation in the year before the current mental disorder can be rated. This system was designed to allow a diagnosis to be made that contains as much information as possible, whereby the relevant aspects are recorded separately in order to increase the diagnostic reliability on the one hand, and to allow recognition of new associations between the individual aspects on the other. With respect to the syndrome diagnosis on Axis 1 it is noteworthy that this does not represent at all a grammalogue for the psychopathological symptoms but that in many cases it includes hypotheses about aetiology and course. Thus for example "schizophrenic disorder" can only be diagnosed on

Axis I if an organic brain disease has been excluded. The syndrome angle was therefore obviously not consistently considered when the categories on Axis I were determined. Further developments of this system are DSM-III-R (American Psychiatric Association (APA) 1988) and the now valid DSM-IV (American Psychiatric Association (APA) 1994).

The most important advance in the DSM-III system and its successors is without doubt the considerable operationalisation of the diagnostic terms (see below). The ICD wants to continue this principle with its "diagnostic guidelines" and "research criteria", which are given in addition to the general description of a disorder, in order to improve the reliability of the clinical diagnosis. When the most recent, tenth, revision of the ICD was developed (World Health Organization (WHO) 1992) an attempt to achieve the greatest possible compatibility with the DSM-IV was made.

Improvement of the reliability of psychiatric diagnosis by standardisation

Besides the natural, gradual improvements in the validity of the classification of mental disorders as described in the above sections on syndromatology and nosology, it was especially important to improve the reliability of psychiatric diagnoses. The poor reliability of clinical-intuitive diagnosis in psychiatry, particularly before the introduction of the ICD, has been demonstrated in numerous studies (see Möller and von Zerssen 1980, 1984). This becomes especially apparent when Kappa coefficients are chosen as a measure of reliability instead of percentages of agreement or contingency coefficients, which overestimate the reliability. Kappa coefficients correct for chance agreements related to the frequency of certain diagnoses (Cohen 1968; Spitzer and Fleiss 1974; Bartko and Carpenter 1976).

Some of the factors responsible for discrepancies in psychiatric diagnosis are as follows: differences in recording and description of symptoms, in the assignment to syndromatological and nosological units, and in classification systems, etc. Various methods to investigate reliability allow the special shortcomings to be estimated. Common methods to analyse reliability are: evaluation of the agreement between specialists in the diagnosis of concrete patients (Zubin 1967; Katz et al. 1969; Kendell et al. 1974; Klug et al. 1979), evaluation of the agreement between specialists in the diagnosis of psychopathological findings defined on rating scales (Schmid et al. 1974; Jakubaschk and Werner 1976), comparison of the frequency of psychiatric diagnoses in comparable patient samples (Cooper et al. 1972; von Cranach and Strauss 1978).

While most of these evaluations are related to reliability shortcomings between diagnosing physicians on the national level, some large international studies indicated that there are also reliability shortcomings on an international level (Cooper et al. 1972; World Health Organization (WHO) 1973; Kendell et al. 1974). Certain diagnostic stereotypes became apparent in these studies, for example in the sense that British psychiatrists showed a bias towards depression while the Americans were biased towards a diagnosis of schizophrenia.

The older reliability studies were performed before the introduction of the ICD and DSM. They therefore no longer do justice to the current situation. The reliability values for inter-rater agreement within an institution achievable after introduction of the ICD under conditions of routine clinical diagnosis, without application of standardised instruments of evaluation, can be seen from a study performed at the Max-Planck-Institute for Psychiatry (Krauss 1974; Möller and von Zerssen 1980). This study mostly showed satisfactory agreement with respect to the main diagnostic groups, while great divergences became apparent in the subgroups, for example in the categorisation into endogenous and neurotic depression.

The main aim of the attempts in recent decades to standardise psychiatric diagnoses – apart from the worldwide standardisation of the classification system – was, on the one hand, the standardisation of recording and describing of clinical signs and, on the other hand, the standardisation of the syndromatological and nosological characterisation. Great efforts were made to achieve a precise determination of the meaning of psychiatric symptom concepts and a standardised recording of clinical signs. As there are no generally obligatory definitions for many symptom concepts to date, these have to be appended as glossaries to instruments for recording psychiatric symptoms, as is the case in the documentation system of the Working Group on Methodology and Documentation in Psychiatry (AMDP; Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie 1995). A reduction of inter-individual differences in the recording of symptoms can be achieved with standardised rating scales (Möller and von Zerssen 1983; Möller 1989). Besides the AMDP system (Baumann and Stieglitz 1983) the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) and the Inpatient Multi-dimensional Psychiatric Scale (IMPS; Lorr 1974; Hiller et al. 1986) are particularly well known. When the raters are given joint training for these standardised rating scales an especially good inter-rater agreement can be achieved (Heimann et al. 1977). Fully structured interviews, which allow hardly any

room for different styles of exploration, are even more favourable under reliability aspects; these include the Present State Examination (PSE; Wing et al. 1972) and the Diagnostic Interview Schedule (DIS), which was developed in conjunction with the DSM-III (Robins et al. 1981; Wittchen et al. 1985), as well as the Structured Clinical Interview for DSM-III revised (SCID; Williams et al. 1992). However, because of the length of time required to apply these instruments they are not suitable for routine care and can only be used in the frame of extensive research projects. Another disadvantage is that some of the scales, such as the DIS and its successor the CIDI, were developed for trained non-psychiatrists in the context of epidemiological studies so that they do not give psychiatrists the opportunity to bring their special expertise to bear.

Although systematic observations of behaviour and psychological tests are a very good means of recording the facts to be evaluated, so far they have not been used a great deal in psychiatric classifications. This is related, among other things, to the fact that the constructs they record do not achieve the degree of complexity of traditional clinical constructs.

The fact that such a standardisation of symptom description alone results in a significant improvement of the reliability of psychiatric diagnoses (von Cranach and Strauss 1978), even on an international level, was confirmed by two large international research projects: the United States–United Kingdom Project (Cooper et al. 1972) and the International Pilot Study of Schizophrenia (World Health Organization (WHO) 1973). The degree to which inter-rater reliability can be improved by standardised recording and description of symptoms with the PSE became clear from the study by Bronisch et al. (1982). There was a large agreement between the diagnoses made after standardised evaluation with the PSE, with a diagnostic categorisation into 11 categories, demonstrated by a Kappa score of 0.88.

In order to achieve a further improvement of nosological diagnoses, standardising the diagnostic assignment steps in addition to the recording and description of symptoms was attempted. Glossaries represent a first attempt to standardise nosological categorisation, for example the international glossary for the psychiatric part of the ICD (World Health Organization 1977) 1992). However, this only solves part of the problem: such a glossary does not define inclusion and exclusion criteria precisely enough for a nosological categorisation. An improved standardisation of nosological categorisations can be achieved by defining clear inclusion and exclusion criteria for every diagnosis according to the following

principle: in order to make Diagnosis D, the patient must present with Symptom A together with one of the symptoms from the series B, C and E, but Symptoms P and O may not be present. The so-called Feighner criteria (Feighner et al. 1972) proceed according to this principle, as well as the Research Diagnostic Criteria (RDC; Spitzer et al. 1978), which are a further development of the Feighner criteria and the DSM-III (American Psychiatric Association (APA) 1980) and which, in contrast to the other two systems, allow all psychiatric disorders to be diagnosed. It could be shown that merely the application of the RDC resulted in a significant improvement of the psychiatric diagnoses compared to a categorisation based on definitions in the DSM-III, and that the reliability scores could be even further improved if the related standardised rating instrument, the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer et al. 1975, 1978; Luria and Guziec 1981), developed by the same working group, was applied. The inter-rater reliability for all diagnoses had a Kappa score higher than 0.75. In order to allow the DSM-III to be applied for routine diagnoses, inclusion and exclusion criteria had to be modified from those in the RDC to give greater flexibility since otherwise too large a percentage of patients could not be categorised. The fear that the precision required for scientific purposes of categorisation would suffer from the greater flexibility was unfounded in the face of several large inter-rater reliability studies with DSM-III (Spitzer et al. 1979).

The introduction of computers into psychiatric diagnosis meant that more complicated algorithms could be applied than possible in the operationalisations described above (Fleiss et al. 1972; Schmid et al. 1974; Spitzer et al. 1974; Schubo et al. 1975). Thus, all the information from rating scales of psychopathological features, together with additional anamnestic and other information, can be processed by computer. For example, in the CATEGO program (Wing et al. 1974; Wing 1977), syndrome profiles are derived from PSE findings, which are then processed in a further step to achieve a nosological diagnosis in which additional information about psychopathological peculiarities in earlier phases of the illness as well as aetiological factors is included. The usability of this procedure was demonstrated in various large research projects (Scharfetter et al. 1976; von Cranach and Strauss 1978; Bronisch et al. 1982), among others in the United States–United Kingdom Project (Cooper et al. 1972) and the International Pilot Study of Schizophrenia (World Health Organization (WHO) 1973) mentioned above. However, apart from the CATEGO System such time-consuming and, as

far as the computer technicalities are concerned, complicated approaches are much less common today than operationalised diagnoses. In the meantime the operationalised procedures, e.g., DSM-III, DSM-IV and ICD-10 have also been computerised using relevant evaluation instruments. Over the last decade a series of fully structured evaluation and diagnosis instruments have been developed which refer to ICD-10 or DSM-III-R/DSM-IV diagnoses, or both: the Composite International Diagnostic Interview (CIDI; Wittchen and Semler 1991), the Structured Clinical Interview for DSM-III (SKID; Wittchen et al. 1991) and the Schedules for Clinical Assessment in Neuropsychiatry, which is based on PSE classes (SCAN; World Health Organization (WHO) 1991).

Some of the diagnostic constructs in the DSM-III and DSM-IV systems deviate considerably from those in the ICD-9 or ICD-10. This is also the case in the relationship with some other traditional classification systems. Based on the train of thought that perhaps each of these systems could be more valid under certain aspects, some of which may as yet be unknown, a so-called polydiagnostic approach has been advocated (Brockington et al. 1978; Kendell 1981; Philipp et al. 1986a,b; Katschnig and Simhandl 1987; Möller et al. 1988). In such an approach, a series of different diagnostic criteria are applied simultaneously, making it possible to compare one set of study results with another in which at least one of the diagnostic systems was also applied. Furthermore, it allows various validity aspects of the respective diagnosis system, e.g., relationship to biological deviations from the norm, relationship to treatment success, relevance for long-term prognosis (Helzer et al. 1981; Katschnig et al. 1986; Möller and von Zerssen 1986; Möller 1987) to be evaluated. In the long term this could result in more valid diagnostic concepts. Meanwhile, unfortunately, the increasing dominance of DSM-III-R/DSM-IV and ICD-10 has reduced the importance of this polydiagnostic approach.

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

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LETTER

Regarding open access to scientific journals

GUSTAVO A. DELUCCHI

Instituto de Docencia e Investigación en Psiquiatría, La Plata University School of Medicine, La Plata, Argentina

Letters published in this Journal do not necessarily reflect the opinions of the Editors or the Editorial Board.

Dear Editor,

This letter is in response to your invitation to a lively discussion regarding the pros and cons of free availability of online journals.

I agree that having open access to scientific journals helps to speed the dissemination of information. On the other hand, I also agree that somebody must pay the costs.

Living in an undeveloped/developing country like Argentina, it is almost impossible to pay subscription to international journals, therefore I am very grateful to publishers who open their journals to internet connections in such countries, or who allow us to read entire articles a certain period of time after publication.

On the other hand, not only do I not blame the journals that do not have this policy, but I also pay some subscriptions; of course, I wish I could afford more journals than I currently subscribe to.

So, after thanking the WFSBP for letting us have access to *The World Journal of Biological Psychiatry*,

and also for sending the printed version free of charge to the Department of Psychiatry of our University, my conclusion is that if the publication of a journal is the primary source of obtaining funds, it sounds logical that you restrict the access, although it is hard to believe that the Federation will increase significantly the amount of subscriptions from poorer countries.

On the other hand, if the funds that would hypothetically come from increased subscriptions are not needed to maintain the Federation, it seems that you could keep an open access, at least for those parts of the world that are not going to be able to pay the subscription.

Once again: Thank you for helping increase the amount of scientific knowledge in places where it is difficult to obtain.

Sincerely yours
Dr. Gustavo A. Delucchi



WFSBP – LINF Sponsorship Award

In co-operation with WFSBP, the Lundbeck International Neuroscience Foundation (LINF) is offering 3 'Sponsorship Awards' to selected individuals to attend a Lundbeck Institute Seminar, which is held in Denmark.

The *LINF Sponsorship Award* is intended to bridge clinical management and research in biological psychiatry.

What does the winner receive?

The winners will be announced and presented at the opening ceremony at the WFSBP Congress in Vienna 28 June 2005, and a plaque will be presented either to them or to the president/vice president of the relevant national societies.

The *LINF Sponsorship Award* consists of participation in a one-week evidence-based medicine seminar at the Lundbeck Institute in Denmark with reimbursement (equivalent of 3000 Euros) for

- Seminar fee
- Travel
- Accommodation and meals

The three award winners can participate in any of the four one-week seminars according to their main interest. The seminars are held in Skodsborg near Copenhagen, and the topics to choose from are as follows: Mood Disorders, Schizophrenia, Anxiety Disorders and Dementia and Depression in Old Age. Please see www.luinst.org to learn more about the seminars.

Who is eligible?

Candidates are members of the Federation who are potential opinion leaders within the above-mentioned areas, who would like to get an evidence-based update on clinical decisions within the chosen field. They should commit to continue to carry out courses on the subject (with the help of the Lundbeck Institute) when they return from the seminar (the 'cascade' principle).

Each national society can submit up to two candidates and send their CVs along with a short letter stating their intention to carry on what they will be learning at the courses to their colleagues at the relevant places.

Guidelines

- The LINF Sponsorship Award will be awarded to a person regardless of nationality, sex or race.
- The nominees must be within a university, institute or any other acknowledged scientific institution independent of the pharmaceutical industry.
- The nominees must be certified psychiatrists interested in evidence-based medicine and clinical decision-making and have experience in clinical research or educational activities. The nominees must not be more than 40 years of age in 2005.
- The nominees should be proposed by one of the national societies associated with the WFSBP.

Nominators should submit:

- a) A letter of recommendation from the national society
- b) CV of the applicant
- c) Letter of intent to enroll in the 'cascade' process (up to 250 words)

Jury – LINF Sponsorship Award

The jury will be composed of:

Anders Gersel Pedersen – LINF

Carlos Hojaij – President of WFSBP

Joseph Zohar – Chairman of Education Committee, WFSBP

Siegfried Kasper – Local Organizing Committee, WFSBP Congress, Vienna

DEADLINE

To submit a nomination, please send seven (7) copies of the application material in English by 30th April 2005 to:

WFSBP Global Headquarters, Attn.: LINF Sponsorship Award, Avenue de Tervueren 300, B-1150 Brussels, Belgium
Tel: +32 2 743 15 80. Fax: +32 2 743 15 50

Note: Please send application CC to the chairman of the education committee, either via e-mail or mail:

E-mail: jzohar@post.tau.ac.il

Mailing Address:

Prof. J. Zohar, Chaim Sheba Medical Center, Division of Psychiatry, 52621 Tel-Hashomer, Israel

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