

The World Journal of Biological Psychiatry

VOLUME 4

Number 3

July 2003



**The Official Journal of the World Federation
of Societies of Biological Psychiatry**

The World Journal of Biological Psychiatry

ISSN print edition 1562-2975

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Printers

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Subscription Information

- Volume 4 of The World Journal of Biological Psychiatry (ISSN print edition 1562-2975) is printed in 4 issues.
- The subscription price of Volume 4 (which excludes postage) is £140 net (USA, Canada and Mexico US\$240) for institutions; £70 net (USA, Canada and Mexico US\$120) for individuals. Single parts cost £38 net (USA, Canada and Mexico US\$64) plus postage.
- Orders, which must be accompanied by payment, may be sent to the WFSBP Administrative Office, Journal Department, c/o Northern Networking Ltd, 1 Tennant Avenue, College Milton South, East Kilbride, Glasgow G74 5NA, Scotland, UK. EU subscribers (outside the UK) who are not registered for VAT should add VAT at their country's rate. VAT registered subscribers should provide their VAT registration number.
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Editorial

Neurotransmitters, Neurosteroids and Neurotrophins: New Models of the Pathophysiology and Treatment of Depression

A common notion underlying our understanding of major depression and leading to the development of antidepressant drugs is that a functional decrement in central nervous system (CNS) monoamine activity is a key alteration and that antidepressants must increase intra-synaptic monoamine concentrations to be effective. Indeed, the so-called “biogenic amine” or “monoamine” hypothesis of affective disorders was derived by extrapolating from the presumed mechanism of action of drugs that treated or provoked affective symptoms (Schildkraut and Kety 1967). In turn (and in what may have been an unfortunate example of circular reasoning), antidepressant drug development has primarily focused on enhancing, or making more selective, such actions on monoamines. In this Editorial, we propose that diminished CNS monoamine activity represents one route to developing major depression (Charney 1998), but not the only one. Similarly, we propose that monoamine-enhancing actions are one route to successful antidepressant action but not the only one. To the extent these possibilities are true, clarifying alternative biological abnormalities in major depression and/or identifying biologically distinct subgroups of patients should permit more effective and rational pharmacotherapy.

Limbic-hypothalamic-pituitary-adrenal axis: CRH and cortisol

The most well-replicated biological abnormality in major depression is hyperactivity of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis, and normalization of LHPA axis activity may be a prerequisite for stable remission in hypercortisolemic depressives (reviewed in: Murphy 1991). Traditionally considered a reflection of stress or of CNS neurotransmitter changes which, themselves, were more closely related to the aetiology of depression, the LHPA axis changes in major depression are now being seen as directly contributing to the pathogenesis of the depressed state, at least in some patients (Murphy 1991; Reus and Wolkowitz 2001; Wolkowitz et al. 2001; Wolkowitz and Reus 1999). Multiple mechanisms exist at different levels of the LHPA axis whereby LHPA over-activity may initiate, perpetuate or alter the presentation of major depression. For example, centrally-active corticotrophin-releasing hormone (CRH) may be directly anxiogenic and depressogenic, causing (in animals injected intracerebroventricularly with CRH) fearfulness, disturbed sleep, diminished reproductive activity and diminished food intake (Dunn and Berridge 1990). Increased production of CRH may be a primary deficit in depression or may be secondary to an alteration in corticosteroid signalling (Holsboer 2000). Prolonged elevations in cortisol levels may also contribute to depression: cortisol, via classic genomic mechanisms, alters the transcription and synthesis of proteins pivotal to monoamine homeostasis. For example, over-exposure to corticosteroids may promote serotonin system down-regulation, whereas anti-glucocorticoid treatment may have antidepressant effects via increases in serotonin sensitivity (reviewed in: Reus and Wolkowitz 2001; Wolkowitz et al. 2001). Over-exposure to glucocorticoids may also prove neuroendangering or neurotoxic to the brain (Sapolsky 2000). These effects are, in part, secondary to excitotoxic nerve damage and decreased release of neurotrophic factors, mechanisms that may point to novel antidepressant strategies, as discussed below. The neuroendangering/neurotoxic potential of glucocorticoid over-exposure has been conclusively demonstrated in several animal species, and suggestive evidence in support of this exists in humans (McEwen and Magarinos 2001; Sapolsky 2000). Patients with Cushing's disease, for example, demonstrate diminished hippocampal volume, which at least partially resolves upon correction of the hypercortisolaemia (Starkman et al. 1999). Patients with major depression also exhibit decreased hippocampal volume, proportionate to their lifetime days of depression (Sheline et al. 1999), but it is unknown whether this is related to cumulative exposure to cortisol and whether antidepressant treatment abrogates the volume loss. Antidepressant medications, regardless of chemical class or nominal mechanism of action, up-regulate brain glucocorticoid receptors (Barden et al. 1995; Holsboer 2000). Such effects may represent a novel and pivotal common mechanism of action of antidepressants, since up-regulation of glucocorticoid receptors enhances the LHPA axis's ability to recognize and appropriately respond to elevated glucocorticoid levels (i.e., it sensitizes and normalizes negative feedback responsiveness) (Barden et al. 1995). Consequently, inappropriate CRH release is curtailed (theoretically producing antidepressant or anti-anxiety effects), and cortisol levels are normalized (theoretically restraining abnormal genomic regulation and protein synthesis, diminishing cortisol's negative effect on serotonin system activity, and preventing further hippocampal damage). In support of such a mechanism of action of antidepressant drugs, drugs that curtail glucocorticoid activity but that have no direct effects on monoamines (e.g., glucocorticoid biosynthesis inhibitors (Reus and Wolkowitz 2001; Wolkowitz and Reus 1999), steroid receptor blockers (Belanoff et al. 2002) and CRH-1 receptor

antagonists (Holsboer 1999)) have shown preliminary evidence of antidepressant efficacy in some patients. In the future, interventions that directly target the corticosteroid receptor and CRH genes may prove to be even more selective and effective means of therapeutic intervention (Muller et al. 2002).

Neurosteroids

Although cortisol is the most widely studied steroid in depression, numerous other adrenal steroids are biologically active in man (Murphy 1991). Further, a recently identified class of steroid hormones – “neurosteroids” – exists that is synthesized *in situ* in brain, has rapid (non-genomic) effects at classical neurotransmitter receptors and has potent behavioural activity (Rupprecht 2003; Rupprecht and Holsboer 1999). Although the study of such steroids and neurosteroids in major depression is in its infancy, interesting and suggestive leads are accumulating. Dehydroepiandrosterone (DHEA), together with its sulphated metabolite DHEA-S, is interesting to consider for several reasons (reviewed in Wolkowitz and Reus 2000): (1) DHEA(S) levels markedly decrease with age in both men and women, (2) DHEA(S) levels increase in response to acute stress, in parallel with cortisol, but markedly decline with chronic stress and with chronic illness, even though cortisol levels may remain elevated, (3) DHEA(S) appears to exert significant anti-glucocorticoid activity, perhaps serving to constrain acute stress responses and to offset deleterious effects of hypercortisolaemia. For example, in pre-clinical models, DHEA(S) prevents glucocorticoid and excitotoxicity-induced hippocampal damage. (4) Cross-sectional and longitudinal studies have noted relatively higher DHEA(S) levels (or higher DHEA(S)/cortisol ratios) in individuals who are physically and mentally healthier or who exhibit greater longevity, but these findings have not been uniformly replicated. Patients with major depression have been found to have low, high or unaltered levels of DHEA(S), compared to matched controls, and the reasons for these discrepancies are not yet apparent. Nonetheless, emerging double-blind, placebo-controlled trials suggest that DHEA has significant antidepressant effects in patients with major depression (Wolkowitz et al. 1999), midlife-onset dysthymia (Bloch et al. 1999), and schizophrenia (Strous et al. 2003).

Another neurosteroid under active investigation is 3α , 5α -tetrahydroprogesterone (allopregnanolone). Allopregnanolone is a potent endogenous agonist of the GABA-A receptor, and it may play a role in endogenous stress relief and in multiple neuropsychiatric conditions (Rupprecht 2003; Rupprecht and Holsboer 1999). In addition to non-genomic (cell surface receptor-mediated) effects, allopregnanolone and certain other neurosteroids can enter the cell, where they are oxidized to substances that bind cytosolic progesterone receptors, leading to genomically-mediated effects, such as alterations in GABA-A receptor subunit composition, decreased expression of genes coding for CRH and increased expression of genes coding for proteins involved in myelin repair (reviewed in: Rupprecht 2003; van Broekhoven and Verkes 2003). Untreated patients with major depression have low plasma (Romeo et al. 1998; Strohle et al. 1999) and CSF (Uzunova et al. 1998) levels of allopregnanolone, and allopregnanolone levels increase in response to antidepressant treatment (Romeo et al. 1998; Strohle et al. 1999; Uzunova et al. 1998); these increases parallel clinical improvement in depressed patients (Uzunova et al. 1998). One mechanism by which certain antidepressants increase allopregnanolone levels is increasing the oxidative efficiency of 3α -hydroxy-steroid dehydrogenase (HSD), the enzyme that converts dihydroprogesterone to allopregnanolone (Griffin and Mellon 1999). This effect may represent an important and novel mechanism underlying the antidepressant and anti-dysphoric effects of SSRI antidepressants (Guidotti and Costa 1998). Other neurosteroids that may be involved in the pathogenesis of depression and anxiety disorders and in the therapeutic effects of antidepressants (e.g., 3α , 5α -tetrahydrodeoxycorticosterone [THDOC] [a GABA-A receptor agonist] and 3β , 5α -tetrahydroprogesterone as well as pregnenolone and pregnenolone sulfate [GABA-A receptor antagonists]) are beginning to be studied (Meieran et al. In Press; Rupprecht 2003; Strohle et al. 2003; Strohle et al. 1999; van Broekhoven and Verkes 2003).

Neurotrophins

Perhaps the most revolutionary and exciting new theory of depression and of antidepressant drug action was promulgated by Duman and colleagues (Duman et al. 1997). In this model, based on pre-clinical data, stress (as well as increased glucocorticoid hormone levels and decreased serotonin and norepinephrine levels) can lead to altered intra-neuronal second messenger signalling, culminating in a diminution of brain trophic factors, such as brain-derived neurotrophic factor (BDNF). Such

effects could inhibit ongoing neurogenesis in the hippocampus (and to a lesser extent the prefrontal cortex) and could conceivably contribute to the hippocampal volume losses seen in some depressed patients and in patients with Cushing's disease, described above. Loss of hippocampal neuronal cells might provoke certain cognitive and emotional symptoms of major depression (Reid and Stewart 2001), although a direct role of hippocampal dysfunction in major depression remains to be demonstrated. According to Duman and colleagues' hypothesis, antidepressant-induced increases in hippocampal BDNF levels can blunt the ability of chronic stressors (or glucocorticoid excess) to damage vulnerable neurons (Duman et al. 1997). Interestingly, direct infusion of BDNF into rat brain has antidepressant-like effects (Siuciak et al. 1996), and chronic treatment with all known classes of antidepressant medications (e.g., tricyclics, SSRI's, MAO-I's, lithium) significantly increases hippocampal BDNF expression in rats. These increases parallel the time course of clinical response to such antidepressant drugs in depressed patients. Emerging human data support the relevance of BDNF for clinical depression. Depressed patients have low serum levels of BDNF, and BDNF levels are inversely correlated with the severity of depressive symptoms (Karege et al. 2002; Shimizu et al. In Press); the relationship of serum BDNF levels to brain BDNF levels, however, is unknown. Lastly, antidepressant-treated depressed patients, compared to untreated ones, have relatively higher hippocampal levels of BDNF at autopsy (Chen et al. 2001). Antidepressants, therefore, may normalize hippocampal levels of BDNF; this might lessen the hypothesized neurotoxic sequelae of depression.

Glutamate

Among the mechanisms by which stress and glucocorticoid excess can culminate in neuronal toxicity is excitotoxic injury, mediated by the NMDA receptor (Sapolsky 2000). Glutamate antagonists acting at the NMDA receptor protect vulnerable neurons against a variety of insults, including stress and glucocorticoid-induced damage; they are also capable of increasing BDNF synthesis and increasing neurogenesis in the dentate gyrus (reviewed in Skolnik 1999). Perhaps through these or other mechanisms, NMDA antagonists may represent another emerging class of antidepressant medication (reviewed in: Krystal et al. 2002; Skolnik 1999). Consistent with an antidepressant effect of NMDA receptor antagonism is the observation that chronic treatment with standard antidepressants alters NMDA receptor subunit composition and dampens regional NMDA receptor function (Skolnik 1999).

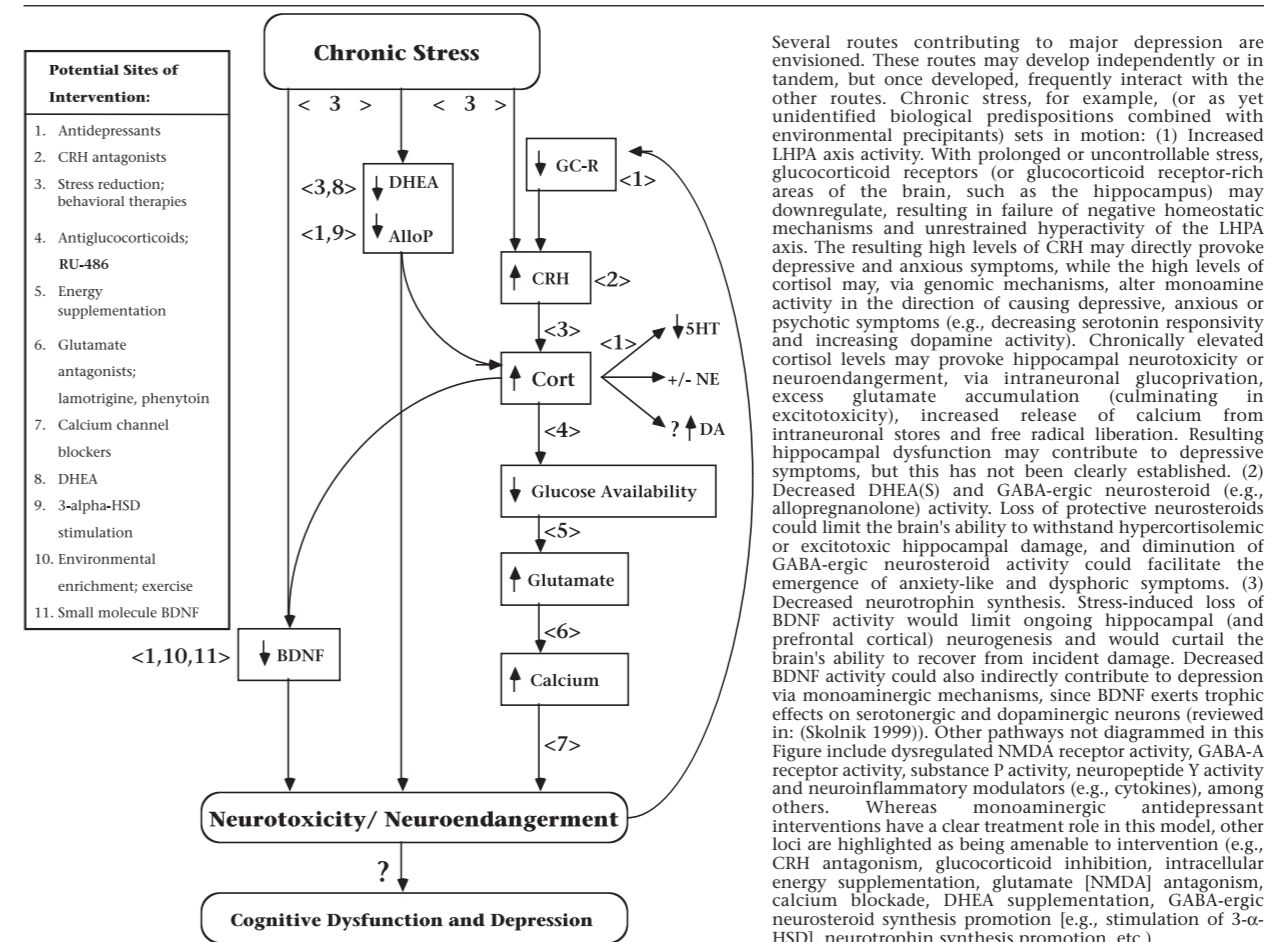
GABA

Multiple lines of evidence suggest an impairment in GABA activity in major depression (reviewed in Krystal et al. 2002). For example, magnetic resonance spectroscopic imaging has revealed decreased occipital cortical GABA concentrations in depressed patients. This abnormality, which co-occurs with increased glutamate concentrations in the same voxels, is seen in unipolar depressed patients, particularly those with psychotic or melancholic depressions, but is not seen in bipolar or atypical depressives (reviewed in Krystal et al. 2002). SSRI's, as well as ECT, eliminate the cortical GABA abnormality seen in depressed patients (Krystal et al. 2002). In addition, as mentioned above, SSRI's (and perhaps other antidepressants) increase brain levels of certain GABA-A receptor agonist neurosteroids, such as allopregnanolone, thereby further enhancing GABA-ergic activity. Lastly, fluoxetine, an SSRI, directly modulates activity of GABA receptors via interactions at a novel modulatory site, increasing GABA receptor response to sub-maximal concentrations of GABA (Robinson et al. 2003).

Table 1

Non-monoaminergic mechanisms of standard antidepressants

1. Increased glucocorticoid receptor binding (resulting in increased sensitivity of glucocorticoid receptors to negative feedback and in decreased CRH and cortisol levels)
2. Increased brain levels of allopregnanolone, a GABA-A receptor agonist neurosteroid (especially SSRI's?)
3. Increased cortical GABA levels (SSRI's and ECT); increased sensitivity of GABA-A receptors to sub-maximal concentrations of GABA (fluoxetine)
4. Increased BDNF levels (resulting in increased hippocampal neurogenesis and in lessened stress-induced decreases in hippocampal neurogenesis)
5. Altered NMDA receptor subunit composition and dampened regional NMDA receptor function



Several routes contributing to major depression are envisioned. These routes may develop independently or in tandem, but once developed, frequently interact with the other routes. Chronic stress, for example, (or as yet unidentified biological predispositions combined with environmental precipitants) sets in motion: (1) Increased LHPA axis activity. With prolonged or uncontrollable stress, glucocorticoid receptors (or glucocorticoid receptor-rich areas of the brain, such as the hippocampus) may downregulate, resulting in failure of negative homeostatic mechanisms and unrestrained hyperactivity of the LHPA axis. The resulting high levels of CRH may directly provoke depressive and anxious symptoms, while the high levels of cortisol may, via genomic mechanisms, alter monoamine activity in the direction of causing depressive, anxious or psychotic symptoms (e.g., decreasing serotonin responsivity and increasing dopamine activity). Chronically elevated cortisol levels may provoke hippocampal neurotoxicity or neuroendangerment, via intraneuronal glucoprivation, excess glutamate accumulation (culminating in excitotoxicity), increased release of calcium from intraneuronal stores and free radical liberation. Resulting hippocampal dysfunction may contribute to depressive symptoms, but this has not been clearly established. (2) Decreased DHEA(S) and GABA-ergic neurosteroid (e.g., allopregnanolone) activity. Loss of protective neurosteroids could limit the brain's ability to withstand hypercortisolemic or excitotoxic hippocampal damage, and diminution of GABA-ergic neurosteroid activity could facilitate the emergence of anxiety-like and dysphoric symptoms. (3) Decreased neurotrophin synthesis. Stress-induced loss of BDNF activity would limit ongoing hippocampal (and prefrontal cortical) neurogenesis and would curtail the brain's ability to recover from incident damage. Decreased BDNF activity could also indirectly contribute to depression via monoaminergic mechanisms, since BDNF exerts trophic effects on serotonergic and dopaminergic neurons (reviewed in: Skolnik 1999)). Other pathways not diagrammed in this Figure include dysregulated NMDA receptor activity, GABA-A receptor activity, substance P activity, neuropeptide Y activity and neuroinflammatory modulators (e.g., cytokines), among others. Whereas monoaminergic antidepressant interventions have a clear treatment role in this model, other loci are highlighted as being amenable to intervention (e.g., CRH antagonism, glucocorticoid inhibition, intracellular energy supplementation, glutamate [NMDA] antagonism, calcium blockade, DHEA supplementation, GABA-ergic neurosteroid synthesis promotion [e.g., stimulation of 3- α -HSD], neurotrophin synthesis promotion, etc.).

Figure 1. Hypothetical interplay of stress-induced steroid, neurosteroid, neurotransmitter and neurotrophin dysregulation, culminating in neuroendangerment or neurotoxicity. (Reprinted with permission from: Wolkowitz et al. 2001)

Major depression may come about as an interplay of dysregulated (and inter-connected) neurotransmitter, hypothalamic peptide, adrenal steroid, neurosteroid and neurotrophic factor activities, some of which may culminate in CNS dysfunction or neurotoxicity (Figure 1). Also, it has become apparent (at least in pre-clinical models) that standard antidepressants share mechanisms beyond the monoamine synapse (Table 1); these alternate mechanisms may prove to be as important, if not more important, than the monoaminergic ones. An emerging model is that: (1) failure to adapt to stress, on a cellular if not a behavioural level, predisposes to or accompanies depression, and (2) medications that facilitate appropriate cellular adaptation or that attenuate the toxic sequelae of maladaptation are effective antidepressants. To the extent this model is true, multiple loci, not directly linked to increases in intra-synaptic monoamine concentrations, should prove useful in treating major depression (Figure 1) (Wolkowitz et al. 2001). Rather than supplanting the monoamine hypothesis, the newer models reviewed here complement it, and in many cases, interact with it. By broadening our mechanistic focus, we will hopefully also broaden our therapeutic power.

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Social Anxiety Disorder

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Summary

Although social anxiety disorder (SAD) is a common and disabling disorder that may occur in different cultural settings, it is under-diagnosed by clinicians. In order to facilitate accurate diagnosis, the clinical features and differential diagnosis of SAD are described, together with useful assessment instruments for clinicians. Aetiological evidence suggests that the causal pathways for SAD include genetic, neurobiological, temperamental and cognitive factors. A range of effective treatments for SAD are available: current findings suggest that the selective serotonin reuptake inhibitors (SSRIs) are the first-line choice of pharmacotherapy for SAD, while several other agents show promise in treating refractory cases; furthermore, SAD responds well to psychotherapeutic interventions such as exposure therapy and cognitive restructuring.

Key words: social anxiety disorder, social phobia.

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Introduction

Although social anxiety disorder (SAD), also known as social phobia, is a severely disabling disorder, it is typically under-diagnosed and under-treated in healthcare settings (Westenberg and den Boer 1999; Katzelnick et al. 2001). This may result from a trend for SAD patients to present for help for co-morbid disorders, such as depression or other anxiety disorders, rather than for social anxiety per se, and a tendency by clinicians to dismiss reported social anxiety as 'normal' shyness. This is unfortunate, particularly in view of recent advances in understanding the pathogenesis and management of SAD. Here, diagnostic issues and assessment procedures relevant to the accurate recognition of SAD are discussed, epidemiological findings and aetiological models are reviewed, and current treatment trends are considered.

Diagnosis and assessment

• Diagnostic criteria

Symptoms of social anxiety disorder have long been described in the psychiatric literature. Social phobia, however, only entered the DSM nosology in 1980 with the publication of DSM III (American Psychiatric Association 1980). Prior to this, social anxiety had been recognized in DSM as a form of general phobia or anxiety neurosis rather than as a qualitatively distinct disorder. The term "social anxiety disorder" may have a number of advantages over "social phobia", including a less pejorative sound (Liebowitz et al. 2000).

The essential feature of SAD is an excessive fear of humiliating or embarrassing oneself while being exposed to public scrutiny or to unfamiliar people, resulting in intense anxiety upon exposure to social performance situations. In addition to the experience of social anxiety, the DSM-IV-TR (American Psychiatric Association 2002) diagnostic criteria further require that the feared situations are either avoided as much as possible, leading to impairments in social and work functioning, or create significant distress. The ICD-10 (World Health Organisation 1992) diagnostic criteria are less strict, requiring the presence of a fear of social situations or fear of humiliation or avoidance in order to make the diagnosis, rather than all three (Tyrer and Emmanuel 1999). Physical manifestations of anxiety in the feared situations include shaky voice, clammy hands,

tremors and, most commonly, blushing. In some cases, panic attacks occur. Associated features of SAD commonly include hypersensitivity to criticism or rejection, a lack of assertiveness, and low self-esteem or feelings of inferiority (American Psychiatric Association 2002).

The focus of the social anxiety varies. For some, anxiety is associated with most social situations (including both formal performance situations such as giving a speech or speaking at a meeting, and informal social interactions such as initiating conversations, attending parties or dating). In such cases, SAD is specified as 'generalized'. For others, anxiety occurs only in specific social situations, such as public speaking, or eating/drinking in public, or writing in public. Research has generally supported the distinct nature of the generalized and specific forms of social phobia, with the former being associated with more severe anxiety and greater impairment than the latter (Turner et al. 1992; Mannuzza et al. 1995).

DSM IV-TR (American Psychiatric Association 2002) notes that shyness and performance anxiety (or "stage-fright") are common in the general population and should not be diagnosed as SAD unless they are associated with clinically significant impairment or marked distress. While there is overlap between SAD and excessive shyness, the two are not the same constructs: people can be extremely shy without meeting a SAD diagnosis or can have specific social phobias (e.g. of writing in front of others) but not be shy in other situations (Chavira et al. 2002). Social phobia symptoms should not therefore be dismissed as normal shyness. Certain forms of SAD are particularly poorly recognized, for example, paruresis or shy bladder syndrome is a performance anxiety that deserves more attention (Vythilingum et al. 2002).

SAD causes a marked reduction in the patient's quality of life and significant disability in functioning, which in turn results in substantial economic costs to both the patient and society (Stein and Kean 2000). It is therefore important for clinicians to accurately diagnose the disorder early in its course, and to treat it timeously.

Diagnostic complications arise from the high degree of overlap between SAD and avoidant personality disorder: Three of the possible criteria for the diagnosis of avoidant personality disorder overlap with those of SAD (Tyrrer and Emmanuel 1999), and co-morbidity of the two disorders is so high (ranging between 22% and 89% (Chavira and Stein 2002)) as to raise questions about the utility of having two separate diagnoses. It has been proposed that avoidant personality disorder and generalized

SAD may not be qualitatively distinct, with the former being simply a more severe variant of the latter (Herbert et al. 1991). DSM-IV-TR (American Psychiatric Association 2002) recommends that in cases of generalized SAD, a diagnosis of avoidant personality disorder should also be considered. Nevertheless, there is growing appreciation that social anxiety may lie along a spectrum of different conditions, including generalized social anxiety, avoidant personality disorder, shyness, non-generalized SAD as well as disorders with heightened social concerns – e.g. body dysmorphic disorder, olfactory reference syndrome, and taijin kyofusho.

In addition to antisocial personality disorder, other common co-morbid conditions for SAD include depression, agoraphobia, panic disorder, generalized anxiety disorder and substance use disorders (Ballenger et al. 1998; Chavira and Stein 2002). Differential diagnosis can be difficult at times, but is usually possible after careful history-taking. Since co-morbid symptoms are important targets for intervention, such careful screening is essential. For example, co-morbid substance abuse not only develops as a way of coping with anxiety symptoms, but may also precipitate anxiety symptoms; this vicious cycle can only be addressed by identifying and treating both components (Lépine and Pélioso 1998). It is crucial to note that co-morbid disorders most often postdate the onset of SAD, and an important question for future research is whether early vigorous treatment of SAD can prevent secondary co-morbidity.

• Assessment measures

There are currently a number of standardized instruments available for assessing SAD. These include clinician-administered diagnostic interviews and inventories, and patient-rated scales. With regard to diagnostic interviews, the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version (ADIS-IV-L (DiNardo et al. 1994)), the DSM-III-based Schedule for Affective Disorders and Schizophrenia, Lifetime Version Modified for the Anxiety Disorders (SADS-LA (Mannuzza et al. 1986)), and the Structured Clinical Interview for DSM, updated to conform to DSM-IV criteria (SCID-I/P (First et al. 1996)), have each demonstrated good reliability (Mannuzza et al. 1986; Skre et al. 1991; DiNardo et al. 1995).

There are two clinician-administered social anxiety inventories that have shown sound psychometric properties and that may be used in treatment studies or in clinical practice to monitor progress. The Liebowitz Social Anxiety Scale (Liebowitz 1987; Heimberg et al. 1999) assesses anxiety and avoidance for 11 social interaction and 13 performance situations,

while the Brief Social Phobia Scale (BSPS) (Davidson et al. 1991; Davidson et al. 1997) assesses fear and avoidance for seven social situations and the severity of four physiological symptoms of anxiety.

Several social anxiety inventories are available to be completed by patients, providing a time-efficient way of assessing the nature and severity of SAD. The 45-item Social Phobia and Anxiety Inventory (SPAI) (Turner et al. 1989) provides information on cognitive, behavioural and somatic responses to a variety of social situations. A cut-off score of 60 is suggested to identify individuals at risk for SAD, and of 80 for distinguishing individuals with SAD from those with other anxiety disorders (Turner et al. 1989). The Social Interaction Anxiety Scale (SIAS) and the Social Phobia Scale (SPS) (Mattick and Clarke 1998) are designed as companion measures to assess fear of social interacting and fear of being scrutinized by others, respectively. Cut-off scores of 34 for the SIAS and 24 for the SPS have been suggested in order to differentiate between individuals with and without SAD (Heimberg et al. 1992), although a formal diagnosis of course requires clinical assessment. Older, pre-DSM-III, patient-rated scales that have also been found useful in assessing SAD symptoms include the Social Avoidance and Distress Scale (SAD) (Watson and Friend 1969) and the Social Phobia subscale of the Fear Questionnaire (FQ-Social) (Marks and Mathews 1979). The recently developed Social Phobia Inventory (SPIN) (Connor et al. 2000) has demonstrated sound psychometric properties and shows promise as both a screening tool (a cut-off of 19 is suggested) and a measure of treatment response.

Given the critical role that has been attributed to negative cognitions in the aetiology and maintenance of SAD (Clarke and Wells 1995; Rapee and Heimberg 1997), instruments for assessing social anxiety cognitions are also an important component of the clinician's assessment repertoire. The Fear of Negative Evaluation Scale (Watson and Friend 1969) and its brief version (BFNE) (Leary 1983), and the Social Interaction Self-Statement Test (SISST) (Glass et al. 1982) are useful in this regard.

The International Consensus Group on Anxiety and Depression (Ballenger et al. 1998) recommend that the following screening questions should be addressed to all patients who present as reticent or shy: (1) Are you uncomfortable or embarrassed at being the centre of attention? (2) Do you find it hard to interact with people? Further diagnostic assessment can then be conducted with patients who answer in the affirmative.

Epidemiology

The prevalence of SAD has most commonly been assessed using two instruments: the DSM-III based Diagnostic Interview Schedule (DIS) (Robins et al. 1981) and the DSM-III-R-based Composite International Diagnostic Interview (CIDI) (World Health Organisation 1990). Rates vary considerably across the two measures: the DIS, which queries only three types of social fears, has yielded substantially lower rates (0.5% to 3.8%) than the CIDI (between 7.2% and 16%), which assesses six types of social fears (Lépine and Pélioso 1999; Chavira et al. 2002).

In the general population the gender ratio is approximately 1.5 to 2 females to 1 male (Schneier et al. 1992; Wells et al. 1994), but in clinical samples there is a more even gender distribution (Boyd et al. 1990; Degonda and Angst 1993). The onset of SAD most commonly occurs before the age of 25 (Schneier et al. 1992; Magee et al. 1996), and the mean age at onset is between 14 and 16 years, a developmental period in which social relationships become more important (Ballenger et al. 1998).

Some cross-cultural variation in the prevalence of SAD is apparent: On the DIS, East Asian populations yield substantially lower prevalence rates than Western populations. Such lower rates may not be specific for SAD, but an alternate explanation is that they reflect culture-specific social fears that are not queried by the DIS (Chang 1997). There is some evidence that patients with taijin kyofusho - where the emphasis is on concerns about offending others rather than concerns about embarrassing oneself - meet modified criteria for SAD (Matsunaga et al. 2001). It is interesting also that a sub-group of these patients show poor insight, raising the question of whether such a form of SAD exists also in the West.

Pathogenesis

What neurocircuits might be involved in mediating social anxiety? Given work in preclinical models on the role of the amygdala and related circuits in fear conditioning, it might be suggested that these play a role. While there have been relatively few brain imaging studies of SAD, a number of these have emphasized the role of the amygdala, and a fascinating study recently reported that both an SSRI and CBT normalized activity in the amygdala-hippocampal region (Furmark et al. 2002). Certainly, serotonergic neurons project to neurocircuits involved in fear conditioning; some clinical research suggests serotonergic involvement in SAD, and SSRIs are a useful form of treatment (Stein et al. 2002b).

Other imaging studies have, however, pointed to the involvement of striatal circuits in SAD (Stein et al. 2002b). In particular, molecular imaging research has suggested that dopaminergic striatal circuits may play an important role. This is consistent with a range of findings in preclinical and clinical research, including the response of social anxiety to monoamine oxidase inhibitors which suggest that the dopaminergic system may be involved in mediating social anxiety.

While rodent models of fear conditioning may be relevant to primate anxiety, there may also be important differences. Human and non-human primates need to be prepared to fear angry, threatening or rejecting faces (Mineka and Zinbarg 1995; Stein and Bouwer 1997). However, ethological theories provide a distal explanation (of early evolutionary origins), and require supplementation by work on the proximal mechanisms (e.g. psychobiological factors) involved in mediating SAD. Work on serotonin and dopamine may be relevant, but a range of other systems may also be involved, and much further research is required.

Ultimately, the genetic basis of such systems needs to be established. Family studies suggest that a family history of SAD, and particularly of the generalized subtype of SAD, is an indicator of increased risk for the disorder (Fyer et al. 1993; Stein et al. 1998). One twin study of SAD estimated the heritability of SAD to be 30%-40% (Kendler et al. 1992), while another found only a minimal genetic contribution (Skre et al. 1993). A recent twin study reported that the fear of being negatively evaluated is moderately heritable (Stein et al. 2002c).

When and how is the fear circuit attuned to social anxiety? Early behavioural inhibition may be involved (Kagan et al. 1988). This refers to a temperamental fear of unfamiliar people, objects or situations. In young children, this manifests from as early as 2.5 years in timid, fearful behaviour in a novel environment. Children who have been identified as behaviourally inhibited at age 2.5 years are more likely to be diagnosed with SAD in early adolescence than uninhibited children (Kagan 1994).

Fortunately, desensitization to social anxiety can occur. Fear conditioning models suggest that the medial prefrontal cortex may play a role. Indeed, cognitive models suggest that dysfunctional beliefs serve to maintain SAD. Dysfunctional beliefs commonly held by people with SAD include the assumptions that they will behave in an incompetent or humiliating way in a social situation, and that this will have catastrophic consequences (Clarke and Wells 1995; Rapee and Heimberg 1997).

It is possible that the disorder may develop along different pathways for different individuals (Hirshfeld-Becker et al. 1999). Genetic vulnerabilities may be transmitted in the form of neurobiological abnormalities; temperamental factors such as behavioural inhibition, resulting from genetics or early family environment, may further predispose individuals to social anxiety; individuals with these vulnerabilities may be more susceptible to behavioural conditioning after aversive social experiences; and cognitive distortions (themselves underpinned by biological mechanisms) may maintain SAD. Further work is also necessary to understand variations in the pathogenesis of the spectrums and subtypes of SAD.

Treatment

• Pharmacological treatment

Though under-treated in healthcare settings, SAD is responsive to several forms of pharmacotherapy. The efficacy of the irreversible, nonselective monoamine oxidase inhibitor (MAOI) phenelzine has been established in several double-blind placebo-controlled studies of SAD (Gelernter et al. 1991; Liebowitz et al. 1992; Versiani et al. 1992; Heimberg et al. 1998). However, concerns about tolerability and safety (particularly the risk of hypertensive crisis if dietary restrictions are not adhered to) suggest that the irreversible MAOIs should not be considered as the first-line treatment in SAD (Ballenger et al. 1998; Blanco et al. 2002), although they remain a useful intervention option in treatment-refractory cases. The reversible MAOIs, while presenting significantly fewer side effects, appear to be less efficacious in treating SAD: for example, double-blind, placebo-controlled studies of moclobemide have produced inconsistent results as determined by a meta-analysis (van der Linden et al. 2000). Given their relatively good tolerability, they may be useful in the long-term treatment of those patients in whom they are effective (Stein et al. 2002a).

The selective serotonin reuptake inhibitors (SSRIs) appear to be as effective, but better tolerated, than the irreversible MAOIs, and could be considered as a first-line treatment for SAD (Blanco et al. 2002). Good response rates among SAD patients have been reported for a number of different SSRIs in open and placebo-controlled short-term trials (van der Linden et al. 2000), including some open trials in children (Fairbanks et al. 1997). A number of studies have also demonstrated efficacy of these agents over the longer-term (van Ameringen et al. 2001; Stein et al. 2002d). The SSRIs are relatively well tolerated, and may be effective for both more generalized and less generalized forms of SAD (Stein et al. 2001). They are therefore increasingly viewed as a first-line choice of

pharmacotherapy in SAD (Stein et al. 2001b).

With regard to benzodiazepines, the effectiveness of clonazepam has been demonstrated in several open-label studies and a placebo-controlled study (Davidson et al. 1993), while results of alprazolam studies have been mixed (Blanco et al. 1998). These agents are not, however, effective antidepressants, and given side effects such as sedation, potential problems with withdrawal, as well as the possibility of misuse, they are no longer recommended as first-line treatments for most patients (Ballenger et al. 1998; Stein et al. 2001b).

Beta-blockers have traditionally been prescribed to control anxiety symptoms in specific performance situations. Findings with nonclinical samples of performers (Hartley et al. 1983; Gates et al. 1985) suggest that beta-blockers may be helpful for the specific form of social anxiety disorder. However, in controlled clinical trials, beta-blockers have not demonstrated superiority over placebos (Liebowitz et al. 1992) and are not recommended for generalized social anxiety. Furthermore, a study of pindolol as an augmentation strategy in treatment-refractory SAD did not demonstrate efficacy (Stein et al. 2001c).

Other agents deserve study for SAD, and perhaps particularly for treatment-refractory SAD. Venlafaxine, a serotonin and noradrenaline reuptake inhibitor, has been found useful in SAD patients who did not respond to SSRIs (Altamura 1999). Buspirone was reported useful as an augmentation strategy (van Ameringen 1999). A recent study of gabapentin suggested that this agent may be effective for SAD (Pande et al. 1999), and future study of the combination of SSRIs with anticonvulsants would seem reasonable. Dopaminergic augmentation strategies may also deserve further consideration.

Clinicians struggling to distinguish SAD from avoidant personality disorder should note that the efficacy of both MAOIs and SSRIs in the treatment of the latter disorder has also been demonstrated (Deltito and Stam 1989).

• Psychotherapy

Exposure techniques are based on the assumption that SAD is maintained by conditioned anxiety: avoidance of the feared situation(s) reduces anxiety, thus reinforcing continued social avoidance. Exposure therapy involves repeatedly, and preferably gradually, exposing the patient to the feared situation(s), until he or she becomes habituated to his or her anxiety. Controlled studies indicate that exposure therapy is superior to waitlist, pill

placebo and progressive relaxation training, and as effective as social skills training and cognitive therapy (Oosterbaan and van Dyk 1999; Turk et al. 2002).

However, simple exposure to feared situations does not relieve anxiety for all patients with SAD. Cognitive therapy attempts to address the dysfunctional beliefs and assumptions that create anxiety, and is effective both when used alone and in combination with exposure (Oosterbaan and van Dyk 1999; Turk et al. 2002). It is currently unclear whether the combined form is superior to either exposure or cognitive therapy alone, since findings have been inconsistent (Feske and Chambless 1995). While phenelzine has demonstrated some superiority over cognitive behavioural group therapy (CBGT) during treatment and maintenance, CBGT may be more effective in preventing relapse in the long term (Heimberg et al. 1998; Liebowitz et al. 1999).

Relaxation training in combination with exposure, and social skills training (teaching the patient verbal and nonverbal social skills, such as how to improve eye contact, how to communicate feelings, and how to give and receive criticism) through the use of therapist modelling, behavioural rehearsal and social reinforcement, may also be effective in treating SAD (Oosterbaan and van Dyk 1999; Turk et al. 2002).

Given the high rate of co-morbidity between SAD and avoidant personality disorder, clinicians should note that graduated exposure, social skills training and cognitive therapy have also been shown to reduce avoidance behaviours and improve the quantity and quality of social contacts for patients with social avoidant traits (Cappe and Alden 1986; Alden 1989) and for generalized SAD patients with a co-morbid diagnosis of avoidant personality (Brown et al. 1995).

There are relatively few studies that address how best to sequence or combine psychotherapy and pharmacotherapy. While there are theoretical reasons for being wary of the combination of benzodiazepines and exposure, the combination of SSRIs and CBT may be particularly useful in some cases: initial SSRI treatment could speculatively prove useful in decreasing symptoms, while subsequent CBT could be useful in ensuring maintenance after discontinuation of medications.

Conclusion

Although it is under-reported and under-recognized in clinical settings, prevalence studies indicate that SAD is common in the general population, and that its core features

may be found across different cultures. It is therefore important to educate our colleagues and the lay public that clear diagnostic guidelines exist to enable recognition of SAD as a distinct disorder, rather than as a form of normal social anxiety or as an aspect of depression or another anxiety disorder. Distinguishing SAD and avoidant personality disorder remains a challenge even to experienced clinicians, however. Recent advances in SAD have included the development of reliable and valid instruments for assisting accurate diagnosis, the emergence of a number of promising lines of research on pathogenesis, and evidence that SAD responds well to both medication and psychotherapy. Ongoing research on a number of aspects of SAD should further consolidate the ability of clinicians effectively to recognize and treat this disorder.

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No Influence of a Functional Polymorphism within the Serotonin Transporter Gene on Partial Sleep Deprivation in Major Depression

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Summary

Sleep deprivation exerts transient antidepressant efficacy. As a potential mechanism of action an enhancement of serotonergic and dopaminergic neurotransmission within the CNS is discussed. Because genetic variations influencing neurotransmission could have an impact on therapeutic outcome and stability of improvement, we investigated the functional polymorphism of the serotonin transporter (5-HTT) gene, the 5-HTT-linked polymorphic region (5-HTTLPR), to examine the serotonergic pathway.

We included 56 patients with major depression (DSM-IV). Psychiatric ratings including the HAM-D21 and HAM-D6 scale were assessed on the day prior to partial sleep deprivation (PSD) and on day 1 and 2 after PSD and related to the different genotypes. The 5-HTTLPR variants were determined following PCR amplification using genomic DNA.

58.1% of the patients were responders to PSD. A significant overall reduction in depression scores could be observed on day 1. Subdivision according 5-HTTLPR gene variants showed no differences in clinical outcome on day 1. As expected the therapeutic effect of PSD was only transient and most patients experienced an exacerbation of depressive symptoms on day 2. 5-HTTLPR variants had no influence on reduction of depressive symptoms on day 2 or relapse on day 3.

Thus, the previously reported influence of the serotonin transporter gene on PSD outcome in bipolar depression could not be confirmed in unipolar depressed patients

Key words: unipolar major depression, antidepressive therapy, sleep deprivation, 5-HTTLPR gene polymorphism.

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Acknowledgements

This project is supported by the German Ministry for Education and Research within the promotional emphasis 'German Research Network on Depression' (sub-projects 4.3, 4.2 and 6.1). The authors would like to thank Mrs. S. de Jonge, Mrs. A. Johnson and Mr. K. Neuner for expert laboratory assistance.

Introduction

Sleep deprivation (SD) is a well-known nonpharmacologic intervention in the treatment of depression which exerts rapid antidepressant effects with a large variability in both antidepressant intensity and persistence of improvement. An overall response rate of about 60% has been reported in a metaanalysis in more than 1700 patients (Wu and Bunney 1990) who underwent a night of total sleep deprivation (TSD) during which patients are kept awake from 8 a.m. of day 0 until 10 p.m. of day 1. The late night SD from 2 a.m. until 10 p.m., the so-called partial sleep deprivation (PSD), is as effective and rapid as TSD (Schilgen and Tolle 1980), whereas early night SD from 10 p.m. until 2 a.m. has generally shown to be ineffective (Ringel and Szuba 2001). Because PSD is better accepted by depressed patients it has advantages in clinical routine.

The mechanisms of action of SD still remain uncertain. Besides the impact of SD on the hypothalamic-pituitary-adrenal (HPA) axis (Schule et al. 2001), predominantly an enhancement of both dopaminergic (Benedetti et al. 1996; Ebert et al. 1994) and serotonergic neurotransmission (Benedetti et al. 1999) have been discussed.

One possibility to investigate clinically relevant variants in neurotransmitter function is the evaluation of genetic polymorphisms with regard to the therapeutic efficacy of a specific treatment, e.g. SD. Whereas up to the present date functionally active polymorphisms in dopaminergic neurotransmission, such as variants of the dopamine D4 (Serretti et al. 1999) or D3 (Schumann et al. 2001) receptor, could not be identified to significantly influence response to SD, a functional polymorphism in the sequence of the serotonin transporter (5-

HTT) gene – the 5-HTT-linked polymorphic region (5-HTTLPR) – has been shown to predict TSD outcome in bipolar depression (Benedetti et al. 1999): response to TSD was associated with homozygosity for the l-variant. Moreover the presence of one (S) or two (S/S) short alleles has been supposed to be associated with anxiety (Lesch et al. 1996) and affective disorders (Collier et al. 1996).

Therefore, we investigated whether the impact of the functional polymorphism in the 5-HTTLPR on PSD outcome achieved in bipolar patients (Benedetti et al. 1999) can be found correspondingly in our group of unipolar depressed patients.

Methods

• Subjects

We investigated 56 unrelated psychiatric inpatients suffering from major depression according to DSM-IV (American Psychiatric Association 1994). Clinical and demographic characteristics are given in Table 1.

Further inclusion criteria were a score of at least 18 on the Hamilton Rating Scale for Depression (HAM-D21, 21-item-version (Hamilton 1986) and no psychotropic drugs for at least five days prior to inclusion in the study. Accepted was up to 1g chloralhydrate in case of sleep disturbances up to 1 day prior to the study. A history of other psychiatric diagnoses, especially alcohol or benzodiazepine abuse or dependency according to DSM-IV criteria during the 12-month period prior to the study, other neurologic or medical disorders led to exclusion from the study.

Further psychiatric ratings using the HAM-D21,

the HAM-D6 (Hamilton Rating Scale for Depression, 6-item-version; suitable for repeated measurements and detection of rapid mood changes; covers depressed mood, guilt feelings, work and interest (Bech et al. 1975)), Clinical Global Impression scale (CGI) (National Institute of Mental Health 1976) and self rating scales (visual analogue scale) were performed every day between 11 and 12 a.m. prior to PSD (day 0), the day after PSD (day 1), and two days after PSD (day 2). Response to PSD was defined as a reduction of at least 30% in the HAM-D6 score between day 0 and day 1. Relapse following one night of recovery sleep was assumed if there was a deterioration of at least 30% in the HAM-D6 score between day 1 and day 2.

The study protocol followed the Declaration of Helsinki and was approved by the local ethics committee. All patients were included in the study after adequate explanation of the study procedure and after written informed consent.

• DNA analysis

Genomic DNA was isolated from whole blood (5 ml) according to standard procedures using the Qiagen-Kit. PCR amplification of the 5-HTTLPR polymorphism was carried out using the primers and methods described earlier by our group (Bondy et al. 2000). All laboratory procedures and ratings were carried out under single-blind conditions: laboratory personnel was blind against origin of DNA probes and diagnoses, clinical raters were informed about the genotypes after discharge of the patients.

• Statistical analysis

Statistical analyses were performed using SPSS for Windows (Release 11.0.1, SPSS Inc., Chicago, Illinois 60606, USA). The One-Sample Kolmogorov-Smirnov Test was used to confirm normal distribution of HAM-D21 and HAM-D6 scores. Mean differences in demographic and clinical variables between the genotypes were compared using independent samples Student's t-tests and χ^2 -tests. To evaluate significant time effects on HAM-D6 after PSD ANOVA for repeated measurements with time as within subjects factor and genotype as a between subjects factor was performed. An independent samples t-test was performed to detect significant differences in HAM-D mean scores between 5-HTTLPR genotypes. Differences between s-allele carriers and patients homozygous for the l-allele were investigated because prior investigations associated both lower anxiety (Lesch et al. 1996) and better therapeutic outcome (Benedetti et al. 1999) with the absence of the s-allele. Differences on day 1 were investigated to evaluate response, differences on day 2 indicated the extent of relapse. The level of significance was set at 0.05. Presupposing an α of 0.05, a difference in the HAM-D6 score of 5 and a standard deviation of 4.6 with 56 patients, a satisfactory statistical power (Student's t-test) of 0.80 could be reached.

Results

Genotype frequencies of the 5-HTTLPR (Minov et al. 2001) polymorphism were in Hardy-Weinberg equilibrium and were comparable to those already published (Deckert et al. 1997). Genotype frequencies, patient characteristics, HAM-D scores, χ^2 and t-test results are shown in Table 1.

The subdivision of patients according to the genotypes showed no significant differences in treatment procedures, demographic data and clinical variables at the beginning of the treatment. All clinical variables were normally distributed. The repeated measurement ANOVA revealed a significant time effect for both HAM-D21 ($F_{2,56}=17.2$; $p<0.0001$) and HAM-D6 scores ($F_{2,56}=15.3$; $p<0.0001$). Our patients showed a significant improvement on day 1 in both HAM-D21 (t-tested for paired samples: $T_{56}=6.88$, $df=55$, $p<0.0001$) and HAM-D6 ($T_{56}=6.05$, $df=55$, $p<0.0001$) scores. 58.1% of our patients responded to PSD. However, as expected the therapeutic effect was only transient in that 72.2% of the PSD responders (26 out of 36) experienced a relapse of depressive symptoms on day 2, whereas 10 patients remained clinically improved after one night of recovery sleep. The 5-HTTLPR gene polymorphism had no significant influence on HAM-D outcome (HAM-D6: $F_{2,56}=0.022$; $p=0.979$). The Student's

t-test showed no significant impact of the 5-HTTLPR gene polymorphism on both response and relapse measured in HAM-D6 scores.

Discussion

We could not reveal any significant effects of the allelic variation of 5-HTTLPR on response or relapse after PSD in unipolar depressed patients. In contrast, in patients receiving the selective serotonin reuptake inhibitors fluvoxamine (Smeraldi et al. 1998) or paroxetine (Zanardi et al. 2000) a genotype-dependent therapeutic outcome has been observed. Additionally, a better mood amelioration after TSD in bipolar depressed patients who were homozygous for the long variant of the polymorphism (L/L) has been shown (Benedetti et al. 1999). One possible explanation for our divergent results could be the relatively small sample size in our study. Because we could not even detect a trend towards a difference related to the 5-HTTLPR genotype, this explanation seems not to be very likely. Other differences in the design of both studies are the performance of a PSD in our study in contrast to TST in the study of Benedetti et al. (1999). Due to the fact that both designs have proven to be correspondingly effective (Schilgen and Tolle 1980), this explanation also is rather unlikely. A more plausible explanation could be the investigation of different patient populations. It is well-known that unipolar and bipolar depressed patients in spite of all clinical similarities belong to different entities of disorders, at least from a genetic point of view, e.g. bipolar patients have a greater genetic loading for affective disorders than unipolar depressives (Cvijetkovic-Bosnjak 1998). Whether other genetic variations concerning serotonergic pathways of neurotransmission may influence treatment response to or relapse after PSD in unipolar major depression remains to be elucidated.

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Table 1

5-HTTLPR gene polymorphism
Genotype frequencies, demographic and clinical data

	5-HTTLPR genotypes		t-test, χ^2	
	L/L	L/S + S/S	T, χ^2	P
n	21 (36.8%)	36 (63.2%)		
Sex (M/F)	8 / 13	11 / 25	0.3	N.S.
Age (mean±SE)	46.6 ± 3.0	49.4 ± 2.6		
Range	22 - 67	22 - 77	-0.7	N.S.
Age of onset	39.2 ± 3.8	35.8 ± 2.3	0.1	N.S.
No. of episodes	3.8 ± 1.1	3.7 ± 0.7	0.4	N.S.
HAM-D21 (mean±SE)				
day 0	23.8 ± 1.1	23.9 ± 1.3	-0.3	N.S.
day 1	14.5 ± 1.7	16.1 ± 1.5	-0.7	N.S.
day 2	18.4 ± 1.7	20.5 ± 1.4	-0.9	N.S.
HAM-D6 (mean±SE)				
day 0	11.3 ± 0.6	10.7 ± 0.7	0.5	N.S.
day 1	7.0 ± 1.0	7.1 ± 0.8	-0.1	N.S.
day 2	8.8 ± 0.9	9.4 ± 0.8	-0.5	N.S.

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Hepatitis C, Alpha Interferon, Anxiety and Depression Disorders:

A Prospective Study of 71 Patients

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Summary

This article presents a prospective study of 71 patients infected with chronic viral hepatitis C and treated with interferon alpha during one year. The objective was to assess the incidence and predictive factors of anxiety and depression symptoms during and after the therapy.

Each patient received psychiatric assessment before, during and after treatment, with evaluations using Hamilton-anxiety and MADRS scales.

Results confirm the great incidence of depression and anxiety not only during interferon alpha therapy but also after treatment is discontinued. Sleep disorders and MADRS ratings of M4 seem to be predictive of the therapy's side effects.

Thus, there seem to be easily discernable parameters allowing depression and suicidal behaviour to be anticipated. This paper emphasises their possible occurrence after the treatment and, therefore, the need for routine assessments after treatment is discontinued. Teams comprising both hepatologists and psychiatrists should complete these assessments. This shows the necessity of interdisciplinary collaboration treatment of this kind.

Key words: *anxiety and depression disorders, hepatitis C, interferon alpha, prospective study, suicide.*

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Introduction

The hepatitis C virus was identified in the late 1980s. Around 170 million people are infected in the world, with 600 000 in France (Braconnier 1999).

If 20 % of patients recover spontaneously, 80% develop chronic hepatitis C, among whom 15 % proceed to cirrhosis and hepato-cellular carcinoma, within 15 years. For a third of these patients, the source of contamination was unknown, a third were infected after transfusion (before the 1990s), and a third after intravenous injection of drugs.

Interferon Alpha (IFN) is the first licensed treatment, which is used for its antiviral and immunomodulatory properties. Until recently, patients received standard interferon at a dose of three million international units (IU) by subcutaneous injection three times a week for one year, either alone or in association with ribavirin. 20 to 80 % of patients are responders during the treatment, but only 10 to 50 % have a sustained response after treatment, the cut-off of 50 % being obtained with pegylated interferon. This treatment presents numerous side-effects (Renault and Hoofnagle 1989):

- Minor disorders: headaches, influenza-like syndrome, psychological and physical asthenia, digestive disorders, anxiety, irritability, sleeping disorders, reduced attention span (Taruschio et al. 1996b).
- Major disorders: cardiovascular problems, alterations in immunity, depression, delirium, disorientation, suicidal ideation, paranoid ideation (Iancu et al. 1997; Janssen et al. 1994).

The mechanisms of the central nervous system effects of interferon alpha are not known. The treatment can produce electroencephalographic changes, but IFN is a protein that cannot cross the normal and intact blood-brain barrier (McDonald et al. 1987; Mattson et al. 1984). Most side-effects appear in the first weeks of treatment and are highest between the first and the third month (Renault et al. 1987). The severity of symptoms varies with the dose, particularly daily rather than cumulative dose. Anxiety and depression are the most frequent and worrying of the psychiatric effects (7 to 35

% of cases, Table 1) (Hunt et al. 1997; Pariante et al. 1999). Symptoms improve two to three days after a reduction of dose, and resolve typically in some days or a week after the end of the treatment. The chronology of these troubles poses the question of the influence of interferon on mood or anxiety disorders. These major psychiatric side-effects demand a psychiatric evaluation before treatment (Niiranen et al. 1988). The psychiatrist must look at the medical history, treatment taken in the past, and antecedent mood disorders. A distinction must be drawn between physical asthenia and depressive symptoms with sadness, world-weariness, mental and physical debility.

Table 1

Psychiatric side effects with IFN alpha in the literature

Psychiatric side effects	Incidence (%)
Overall	7 - 35
Depression	5 - 15
Suicide attempt	1.5
Suicide	0.4

This treatment is contra-indicated in severe depression, psychosis, addiction disorders, personality disorders (Taruschio et al. 1996a).

Study

• Patients and methods

The aim was to estimate the incidence of anxiety and depressive disorders during and after a treatment by IFN in patients with chronic hepatitis C and to determine related predictive factors.

We included 71 consecutive patients in one year with chronic hepatitis C in whom IFN was indicated. None of them had previously received IFN. Over 48 weeks, they received three to six million IU IFN, by subcutaneous injection three times a week, alone or in association with ribavirin 1g per day by mouth. Patients were assessed monthly by hepatologists for one year and again at M18 (six months after the last injection). They were assessed by the same psychiatrist before treatment began (at M0), during the treatment at M4, at the end of the treatment M12 and six month after the last injection at M18. Two scales were used for the assessments: Hamilton-Anxiety Scale and Montgomery and Asberg Depression Rating Scale.

• Results

Descriptive study

There were 44 men and 27 women. The mean age was 45 years. 41% (28 patients) had a psychiatric history: depression in 24% (16 patients), attempted suicide in 12% (eight

patients), drug addiction in 29%, alcohol disorders in 12%. Antidepressant had previously been prescribed for 16%, and anxiolytics for 22%.

The means of exposure to hepatitis C was known for 80% of patients (40%: transfusion, 40%: intravenous drug abuse).

During treatment, 33% of patients (22 cases) presented psychiatric side-effects. The incidence is greater than that usually described in the literature. Fifteen patients had depression, and for 3 patients the depression was associated with suicidal ideation. The treatment was stopped in 10% of them. (Table 2).

Table 2

Anxiety-depressive symptoms during IFN treatment in our study

Psychiatric symptoms	N (%)	Treatment withdrawal N (%)
Overall	22 (33)	7 (10)
Depression	15 (23)	2 (3)
Depression + suicidal ideation	3 (5)	2 (3)
Suicidal ideation without depression	1 (1)	1 (1)
Other (irritability, anxiety...)	2 (3)	2 (3)
Irritability + suicidal ideation	1 (1)	0 (0)

There was no suicide attempt during the treatment. Many patients reported that the various consultations could have had a protective effect.

We noted a large incidence of the anxiety-depressive effects after the end of treatment. At M18, 8% of patients were still depressed. Eight per cent (four patients) had suicidal ideas and 8% (four patients) had suicidal behaviour. The MADRS score was higher at M4 than at M0 and lower at M18 than at M12 (Figure 1). The Hamilton-Anxiety score was higher at M4 than at M0 and lower at M18 than at M12 (Figure 2).

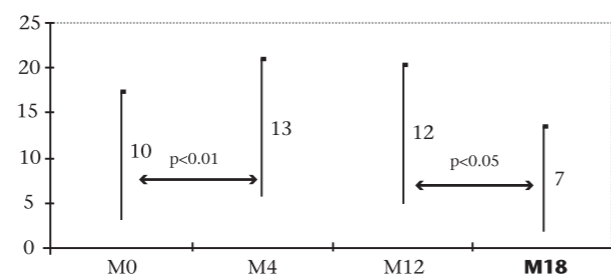


Figure 1

Mean scores of the MADRS during and after IFN treatment (mean, SD)

Predictive study

We investigated the factors that can be used to predict anxiety or depressive disorders during treatment. Univariate analysis is reported in Table 3.

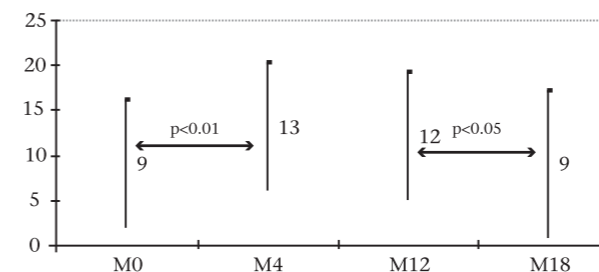


Figure 2

Mean scores of the Hamilton-Anxiety Scale during and after IFN treatment (mean, SD)

Stepwise analysis showed two independent factors: female gender and the MADRS at M4 (score > 15).

Table 3

Predictors of anxiety-depressive symptoms during IFN treatment (univariate analysis)

	Anxio-depressive symptoms		p
	Yes	No	
MADRS score at M4 (mean)	19	11	<0.001
Hamilton-Anxiety at M4 (mean)	12	17	<0.05
Female gender (%)	64	31	<0.05
Prior hypnotic treatment (%)	32	9	<0.05
Prior psychiatric disorders (%)	64	32	<0.05
Sleep disorders during IFN treatment (%)	82	51	<0.05
Personality disorders during IFN treatment (%)	86	60	<0.05
Anxiolytic prescription during IFN treatment (%)	57	20	<0.01
Antidepressants prescription during IFN treatment (%)	52	9	<0.001
Hypnotic prescription during IFN treatment (%)	38	11	<0.01
Withdrawal of IFN treatment (%)	55	27	<0.01
Cause of withdrawal (%)	55	27	<0.01

Univariate analysis of suicidal risk is reported in Table 4. Stepwise analysis showed two independent factors could be used to predict suicidal risk (suicide, suicide attempts and suicidal ideation): an increase in the scores on Hamilton Anxiety Scale between M0 and M4, and sleep disorders.

Table 4

Predictors of suicidal risk during IFN treatment (univariate analysis)

	Suicidal ideas		p
	Yes	No	
*HAM-A M4 (%) : HAM-A changes between M0 and M4	261	78	<0.05
Sleep disorders during the IFN treatment (%)	100	57	<0.05
Hypnotic prescription during IFN treatment (%)	60	16	<0.05
Withdrawal of IFN treatment (%)	100	30	<0.01
Cause of withdrawal (%)	100	30	<0.01

Many patients presented mood disorders or anxiety in spite of discontinued treatment. Prior antidepressant prescription was a significant predictive factor of anxiety or mood disorders after the end of treatment.

Discussion

This study confirms many side effects of IFN:

- The risk of developing depressive symptoms, 33 % in our study. Most of them had no psychiatric diagnosis according to ICD 10 before the treatment. This result suggests that IFN had provoked mood and anxiety disorders. Carpiello (1998) shows that the risk of developing manic syndrome with IFN is higher after a long period of depression because of the dopaminergic activity of IFN. We know that IFN can cause mood disorder in patients without a psychiatric history, but the risk is higher if they do have one. Our study shows that prior antidepressant prescription was a predictive factor for symptoms of depression to persist at the end of treatment.
- The risk of suicide during and after the treatment. Usually (Capuron and Ravaud 1999; Janssen et al. 1994), some patients make a suicidal attempt during treatment. It can be explained by the depression and by the reduction of health-related quality of life in patients with chronic hepatitis C. After treatment, the risk continues (Rifflet et al. 1998). Four patients presented suicidal behaviour during the six months after the end of treatment.

The great incidence of psychiatric disorders with IFN calls for psychiatric assessment during and after the treatment. Psychiatrists must look at the psychiatric history to determine if IFN is or is not indicated and evaluate the risk of mood disorders with IFN, before and during its use. The MADRS score at M4 was a predictive factor for mood disorders during and after treatment had been discontinued. Capuron and Ravaud (1999) assessed ten patients treated with IFN for melanoma with MADRS. They concluded that the effects of IFN on mood depend on the initial affective state of the patients.

However, psychiatrists cannot evaluate all of the patients in whom IFN is indicated. Four predictive factors of suicidal behaviour or depression were observed in our study: female gender, scores on the MADRS at M4, sleep disorders during treatment, and prior antidepressant prescription. These predictive factors are easily determined by hepatologists. Such patients can be selected to undergo psychiatric assessment.

In our study 33% of patients presented mood or anxiety disorders. At the same time, none of them presented with suicidal behaviour during



the treatment and only four after the last injection. We suspect that the repeated psychiatric assessments during treatment could have had a protective effect. Van Thiel et al. (1995) used IFN successfully in patients with hepatitis C who had psychiatric illness. Thirty-one patients were treated by IFN and only two patients had an increase in psychiatric symptoms. According to the last consensus conference, IFN is contra-indicated in patients with psychiatric illness, but regular psychiatric assessment would permit treatment.

Conclusion

This study confirms the high incidence of psychiatric side-effects of IFN occurring not only during treatment as expected, but also after the end of the treatment. For this reason, it is of value to continue psychiatric assessment after the end of the treatment.

The predictors of psychiatric outcome are easily ascertained.

This study shows the necessity of interdisciplinary collaboration between physician and psychiatrist for treatment of this kind.

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Research on Psychoimmunology

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Summary

Several lines of evidence suggest a role for the immune system in the multifactorial pathogenesis of schizophrenia and other psychiatric and neurodegenerative diseases. Later, the role of immune mediators like cytokines became a source of main interest related to the process on inflammation in the CNS. In this article we report the results of our research on cytokines in a different groups of psychiatric patients following their clinical symptomatology and the course of diseases. In particular, we observed a prevalent type 1 cytokine profile in acute multiple sclerosis patients, while IL-10 production predominated in stable multiple sclerosis individuals. The modifications of cytokine profiles observed in schizophrenic patients suggests that clinical improvement is associated with a reduction in the inflammatory-like situation present in those not currently under treatment. Our data on Alzheimer's disease (AD) support the role of the inflammatory process in the pathogenesis of AD and reinforce the hypothesis that the neurodegenerative processes in the AD patients are associated with an abnormal antigen-specific immune response. The activation of immune system mechanisms observed in obsessive compulsive disorders could be due to the combination of endogenous (hormonal alterations associated to the modifications in the hypothalamic-pituitary-adrenal axis) and exogenous (viral or bacterial infections) factors.

Key words: cytokines, schizophrenia, multiple sclerosis, Alzheimer's disease, obsessive-compulsive disorders.

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Introduction

The concept of autoantigenic properties of brain tissue was discussed at the beginning of the 20th Century and Monaenkov later (1963) presented his paper on the 'Factor of individuality in immune processes'.

In the 1980s an interest in immunological research in the field of mental disease appeared in the USA (DeLisi et al. 1984; DeLisi 1987; Ganguli et al. 1987) and by a group of Soviet researchers (Vartanian et al. 1978; Koljaskina et al. 1987).

The development of immunological research in psychiatry has run parallel to that of immunology, reflecting the methodological and theoretical advances made in the latter field.

Three important international meetings focused on viruses, immunology and mental disorder were organized in the years between 1975 and 1991 first in Löwen and then in Montreal through the initiative of Morozov, Lipowsky and Kurstak.

In this field everybody knows the contribution of Professor M. Ackenheil and Professor N. Müller. An International Meeting on Psychoimmunology and Psychopharmacology was chaired by the first author in Milan in 1999.

Psychoimmunology is becoming a very important and fruitful area in schizophrenia where the immunoresponse can also be present in patients with chronic disease, but not clearly in the members in their family (Cazzullo et al. 1998a; Cazzullo 2001)

Later still, the role of immune mediators like cytokines became a source of main interest related to the process on inflammation in the CSM. We devoted a good deal of research to cytokines, especially IL-2, IL-6, IL-12, IL-10 and TNF- α in a different group of psychiatric patients following their clinical symptomatology and the course of their diseases (Cazzullo et al. 1998b).

Basic immunological models

The activation of two different functional compartments is the basis of antigen-specific immune responses.

One is defined as T-helper 1 (TH1), mostly concerned with the activation of cell mediated immunity (CMI); the second is defined as response T-helper 2 (TH2) and is primarily responsible for the stimulation of humoral immunity and the generation of antibodies.

Type 1 cytokines are those that mainly induce CMI. The most important type 1 cytokines are IL-2, IL-12 and g-Interferon (IFN-g). Type 2 cytokines (e.g. IL-4, IL-5, IL-6, IL-10) trigger humoral immunity.

TH1 and TH2 activation, and the secretion of type 1 and type 2 cytokines, are mutually exclusive, as we can realize by the fact that IFN-g blocks the production of TH2 cytokines, while IL-4 and IL-10 suppress TH1 cytokine production.

A disequilibrium in the TH1-TH2 ratio is related to various pathologies such as LES, MS, HIV infection and, possibly, to a number of psychiatric diseases.

• Cytokines

The individual features of various cytokines are as follows.

IL-2 is the principal cytokine responsible for progression of T lymphocytes from G1 to S phase of the cell cycle. IL-2 is produced by CD4+T cells and, in lesser quantities, by CD8+ T cells. IL-2 acts on the same cells that produce it as an autocrine growth factor, and it also acts on nearby T lymphocytes as a paracrine growth factor. IL-2 stimulates the growth of NK cells and enhances their cytolytic function, producing so-called lymphocyte-activated killer (LAK). IL-2 acts on human B cells both as a growth factor and as a stimulus for antibody synthesis.

IL-6 is synthesized by mononuclear phagocytes, vascular endothelial cells, fibroblasts, and other cells in response to IL-1 and, to a lesser extent, TNF. It is also made by some activated T cells; IL-6 can be detected in the circulation following gram-negative bacterial infection or TNF infusion. This cytokine causes hepatocytes to synthesize several plasma proteins, such as fibrinogen, that contribute to the acute phase response. IL-6 serves as a growth factor for activated B cells late in the sequence of B cell differentiation.

IL-10 is produced by activated macrophages, some lymphocytes, and some non-lymphocytic

cell types (e.g. keratinocytes). The two major activities of IL-10 are to inhibit cytokine (i.e., TNF, IL-1, chemokine, and IL-12) production by macrophages, and to inhibit the accessory functions of macrophages in T cell activation. The latter effect is due to reduced expression of class II MHC molecules and reduced expression of co-stimulators, e.g., B7-1 and B7-2. The net effect of these actions is to inhibit both innate and T cell-mediated specific immune inflammation.

TNF- is the principal mediator of the response to gram-negative bacteria and may also play a role in innate immune responses to other infectious organisms. The major cellular source of TNF- is the LPS-activated mononuclear phagocytes, although antigen-stimulated T cells, activated NK cells and activated mast cells can also secrete this cytokine. TNF- is a mediator of both innate and specific immunity and an important link between specific immune responses and acute inflammation. When small amounts of TNF-a are produced, this molecule acts locally as a paracrine and autocrine regulator of leukocytes and endothelial cells: TNF causes vascular endothelial cells to express new adhesion molecules that make the endothelial cell surface become adhesive for leukocytes, monocytes and lymphocytes. TNF stimulates mononuclear phagocytes and other cell types to secrete chemokines that contribute to leukocyte recruitment. This cytokine activates inflammatory leukocytes to kill microbes. At high concentrations TNF- is an endogenous pyrogen, acts on mononuclear phagocytes to stimulate secretion of IL-1 and IL-6 into the circulation, and acts on hepatocytes to increase synthesis of certain serum proteins, such as serum amyloid A protein. Long-term systemic administration of TNF- causes the metabolic alterations of cachexia. Several specific actions of TNF- may contribute to its lethal effects at extremely high concentrations: this molecule reduces tissue perfusion by depressing myocardial contractility.

Methods

• Blood sample collection

Whole blood was collected by venepuncture in Vacutainer tubes containing EDTA (Becton Dickinson Co, Rutherford, NJ). Peripheral blood mononuclear cells (PBMC) were separated by centrifugation on lymphocyte separation medium (Organon Teknika Corp, Durham, NC) and washed twice in PBS. The number of viable lymphocytes was determined by trypan blue exclusion and a haemocytometer.

• In vitro cytokine production

PBMCs were resuspended at 3x10⁶/ml in RPMI 1640 and were either unstimulated or stimulated with LPS (Sigma, St. Louis, MI)

(10 µg/ml), with a pool of 3 different peptides from the b-amyloid protein as follows: b-A: fragment 25-35 (25 mg/ml); b-B: fragment 1-40 (150 ng/ml); b-C: fragment 1-16 (150 ng/ml) (Sigma, St. Louis, MI); or with influenza virus vaccine (A/Taiwan+A/Shanghai+B/Victoria) (24 µg/l; final dilution 1:1000)(Flu) (control antigen) at 37°C in a moist, 7% CO₂ atmosphere. Supernatants were harvested after 48 hours for LPS stimulation and after 5 days of culture for the b-amyloid protein peptides and Flu. Production of IL-2 and IL-10 by PBMCs was evaluated with commercial available ELISA kits (ACCUCYTE, Cytimmune Sciences, Inc, College Park, MD). All test kits were used following the procedures suggested by the manufacturer.

• IL-10 genotyping

Genomic DNA was extracted from EDTA-treated peripheral blood (10 ml) using a standard proteinase K and phenol/chloroform method. The DNA concentration and purity were determined by spectrophotometric analysis. A polymerase chain reaction-sequence specific primers (PCR-SSP) methodology was utilised to assess the IL-10 genotypes. The amplification of the sequence in the promoter region of the IL-10 (polymorphic positions -1082, -819, -592) gene were performed using the Cytokine genotyping Tray Method (One Lambda, Canoga Park, CA, USA); the human b-globin gene was amplified as an internal control of genomic DNA preparation. PCR condition were indicated by One Lambda PCR program (OLI-1); the PCR products were then visualised by electrophoresis in 2.5% agarose gel.

Focus of our research

Our activity has been mainly devoted to the follow topics:

• Multiple sclerosis

Multiple sclerosis (MS) is a chronic neurological disease characterized by multifocal inflammation and damage involving the myelin sheath and the presence of a peculiar psychiatric symptomatology. MS patients present with a variety of clinical patterns, including acute and stable forms. Although the aetiology of MS is still unclear, an immunopathological mechanism, mainly mediated by the activation of cell-mediated immunity (CMI), was suggested long ago (Ferraro and Cazzullo 1948) to be responsible for the destruction of the myelin sheath. Cytokines have been involved in the pathogenesis of MS; thus, increased levels of TNF-a and IFN-g were detected in MS patients with acute disease. Treatment of MS with IFN exacerbates the disease, whereas therapeutic approaches based on the utilization of IFN-a and IFN-b, which are known to be effective in a number of patients, decrease IFN-g production by T lymphocytes, suggesting a direct

pathogenic role of this cytokine. We analysed in vitro antigen- and mitogen-stimulated cytokine in multiple sclerosis (MS) patients with either acute (AMS) or stable (SMS) disease and in healthy controls (HC). We also investigated whether immune responses to human endogenous retroviruses (HERV) could be detected in MS and whether these immune responses would be correlated with disease status by analysing cytokine production after stimulation of PBMC with HERV peptides. Results showed that mitogen-stimulated IL-2 and IFN-g was augmented and IL-10 was decreased in AMS compared to both SMS and healthy controls. Whereas the production of the metabolically active IL-12 (p70 heterodimer), was comparable in SMS, AMS and HC, production of the total IL-12 (p70 heterodimer and the p40 chain) were augmented in SMS compared to both AMS and HC. HERV-peptides IL-2 and IFN-g production was more frequent and more potent in AMS compared to both SMS patients and HC. HERV-specific type 2 cytokine production was more frequent and potent in SMS compared to AMS and HC. Thus a prevalent type 1 cytokine profile was seen in AMS patients, while IL-10 production predominated in SMS individuals (Clerici et al. 1999; Clerici et al. 2001; Ferrante et al. 1998).

• Alzheimer's disease

Recent studies of Alzheimer's disease showed that the deposition of amyloid is one of the critical events responsible for the cerebral damage that causes the onset of disease. The amyloid plaques are characterized by the presence of b-amyloid (Ab) stemming from the cleavage of membrane protein. The immune system could play an important role in the neurodegenerative process associated with cerebral plaques. These inflammatory and immune proteins could stimulate the Ab production, facilitate aggregation and increase toxicity of this protein, causing a rise in the severity of AD pathology. The Ab could stimulate the release of inflammatory and immunologically-active molecules from microglial cells and activated astrocytes. However, there are also studies showing a protective role of the immune system in the development of AD. Microglial cells are able to degrade Ab. Recent observations suggest that autoreactive T cells play a role in the peptide elimination. This mechanism seems to be less effective in the AD patients. Thus a specific immune response to Ab could represent a natural defence mechanism in order to prevent the inflammatory processes associated with the amyloidogenic process. The weakening of the immune response and the failure to eliminate toxic metabolites could be the basis of the cerebral chronic inflammatory process in the AD patients.

We have evaluated cytokine production in 50 AD patients and in 30 healthy subjects of comparable age and sex. The peripheral blood mononuclear cells have been stimulated with lipopolysaccharide (LPS) or with a pool of Ab peptides. The results obtained show an alteration in the immune specific response to b-amyloid, an increase in the pro-inflammatory cytokine production, and a reduced IL-10 production in AD patients. It is noteworthy that IL-10 production results in a potent anti-inflammatory response. Analyses on the alleles of the IL-10 gene revealed that the genotype associated with high IL-10 production is extremely infrequent in AD individuals (2% vs. 28%). The presence of low/intermediate-IL-10-producing genotypes (GCC/ATA; ATA/ATA) was associated with an earlier age at disease onset and (ACC/ACC; ACC/ATA) with an accelerated rate of disease progression. These data shed light on the biology of the inflammatory process involved in the pathogenesis of AD by showing that the presence of low-IL-10-allelic isoforms results in a b amyloid-specific impairment of IL-10 production and is associated with the clinical severity of AD. These data thus suggest that the diminished production of this cytokine would facilitate the activation of the chronic inflammatory processes observed in the progression of AD. These data support the role of the inflammatory process in the pathogenesis of AD and reinforce the hypothesis that the neurodegenerative processes in AD patients are associated with an abnormal antigen-specific immune response. These results lend support to the use of anti-inflammatory compounds in the therapy of this disease.

• Schizophrenia

Alterations in the immune system are found in patients affected by psychiatric disorders and in particular in schizophrenic subjects. Several observations underline that the immune system is involved in these pathologies (Cazzullo 2001). The use of IL-2 in schizophrenic patients can provoke the appearance of symptoms related to the disease, and the severity of the symptoms is correlated with the amount of IL-2 used. In schizophrenic patients there is an increase of serum concentration of the soluble IL-2 receptor, and the concentration of this cytokine is elevated in the CSF of non-treated patients. Additionally, IL-10 production is decreased in paranoid patients. Probably the immune system plays a role in this pathology.

In order to analyze this hypothesis and evaluate if patients with different diagnostic subset (paranoid patients vs. non-paranoid patients) have a different immune response, in our first study, we analyzed cytokine production in 37 patients with chronic schizophrenia and in 40 healthy subjects (Cazzullo et al. 1998b). Results showed that chronic schizophrenia is associated

with an impairment of soluble antigens-stimulated proliferative responses, and with alterations in the production of cytokines (IL-2 and IL-10). Peripheral lymphocytes of patients belonging to the paranoid subset produce less IL-10 than cells of patients without a diagnosis of paranoia. Moreover, type 1 cytokine production (IL-2 and IFN-g) is significantly increased in non-treated schizophrenic patients compared with healthy controls. We have also observed a positive correlation between the PANSS total score and IFN-g production. These data suggest a possible role for the activation of immune response in the generation of psychotic symptoms.

Then we investigated the production of IL-2, IL-4, IL-10 and IFN-g in 12 drug-free and in 12 drug-naïve schizophrenic patients and in 33 healthy controls (Cazzullo et al. 2001). We analysed the modifications of these cytokines during a 3-month period of treatment with risperidone (Cazzullo et al. 2002). The use of risperidone was associated with augmented IL-10 (a suppressor of type 1 cytokines) and decreased IFN-g production. This modification suggests that clinical improvement is associated with a reduction in the inflammatory-like situation present in schizophrenic patients not currently treated.

• Obsessive-compulsive disorders

Based on the immunological alterations that we have observed in schizophrenic patients, we have hypothesised that an impairment of the immunological response could also be present in patients affected by obsessing-compulsive disorders (OCD). Previous studies have demonstrated the presence of high IgG serum concentrations in these patients. Moreover there is an increase of the IgG levels in the CSF of these OCD individuals. Previous studies in which cytokines have been analyzed in OCD patients showed that the plasma concentration of TNF- α plasma is decreased; no differences were detected in the concentration of other cytokines including IL-1b, IL-2 and IL-3 production.

We have analysed type 1 (IL-2, IL-12 and IFN-g) and type 2 (IL-10) cytokine production and the expression of a panel of phenotypical markers in peripheral blood mononuclear of 20 OCD and 12 healthy controls. In particular, eight untreated OCD individuals (NT-OCD) and 12 patients undergoing therapy (T-OCD) have been enrolled in the study. Nine of the analysed patients had psychotic symptoms (P-OCD); these symptoms were absent in the remaining 11 individuals (NP-OCD). The results obtained have demonstrated a significant increase in the absolute number of Natural Killer cells in OCD patients compared to healthy controls ($p < 0.05$). Moreover, the production of IL-2, IFN-g and IL-

10 was significantly increased in P-OCD compared to NT-OCD and T-OCD patients.

The increase of NK cells could indicate the presence of an immune activation in OCD patients. This activation could be due to the combination of the endogenous factors (hormonal alterations associated with the modifications in the hypothalamic-pituitary-adrenal axis) and exogenous factors (viral or bacterial infections).

Conclusions

We would like to recall the intrinsic value of immunological research, especially where it is closely related to the clinical features of various psychiatric diseases.

An open problem is that of the relationship with psychopharmacological agents and the possibility to introduce some immunological mediators.

The second item is in opposition to our law against the use any drugs not specifically indicated for a definite disease.

The future line of research should address any close connection between immunological events and clinical symptomatology, devoting particular attention to patients of a young age.

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Impaired Visuomotor Integration in Acute Schizophrenia

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Summary

Based on the interaction of eye and hand movements a comprehensive index summarizing schizophrenia patients' difficulties during the performance process in Trail-Making Test-B (TMT-B) was developed. The process of TMT-B performance was modelled as a sequence of planning, acting and resting periods in 23 inpatients with acute schizophrenia, 17 inpatients with acute depression and 21 non-psychiatric controls, each assessed at least twice within four weeks. Transition probabilities between these states were calculated and structured by factor analysis.

Throughout their hospital stay schizophrenia patients scored significantly lower than non-patients on a derived "visuo-manuomotor integration factor", characterized by high loadings of transitions between planning and acting periods. A significant negative correlation of this factor with performance time revealed frequent alternations between these two states and thus high factor scores to be a prerequisite for good TMT-B performance. No relationship of factor scores with psychopathology and medication could be found. Depressive patients differed neither from non-patients nor from schizophrenia patients during the acute phase of the illness, but scored significantly higher than schizophrenia patients shortly before discharge. Accordingly, poorer TMT-B performance in schizophrenia patients seems related to impaired planning strategies, which might be a nosologically specific, trait-like characteristic, probably related to neural dysfunctions involving the prefrontal cortex.

Key words: eye movements, hand movements, planning, schizophrenia, trail-making test.

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Introduction

The search for neurobiological correlates of cognitive deficits in schizophrenia patients often suffers from a lack of corresponding objective indicators, which are differentiated enough to be valid correlates for the sophisticated indicators of functional brain activity available at present (Gaebel 1992; Strauss 1994). Especially most neuropsychological tests of so-called frontal lobe functions (e.g. Trail-Making Test) tap a lot of different basic cognitive functions and deliver very global performance measures (e.g. performance time), which do not directly reveal the kind of disturbance in information processing causing the observable impairment and thus are insufficient starting points for the investigation of brain-behaviour relationships. A detailed analysis of the process of task performance, i.e. the contribution of and the synergy between functions, may therefore help to pinpoint the underlying dysfunction and to delineate consistent functional syndromes (Levin et al. 1989).

Recently we reported for the first time data on schizophrenia patients' performance process in a computerized version of the Trail-Making Test (TMT, Reitan 1958; Reischies and Wilms 1989) using concurrent recordings of eye and cursor movements (Wölwer and Gaebel 2002). Related to their often described poorer performance, schizophrenia patients demonstrated time-stable deviances in the performance process especially of test version B (TMT-B): compared with non-psychiatric controls, patients with acute schizophrenia demonstrated longer "planning periods" – as defined by fixations outside the cursor area – which contained more fixations, with increased duration, and which occurred unfavourably often while the cursor rested between targets. Although each of these deviances might reflect a different aspect of the impaired performance process, the pattern of results gave reason to be interpreted within the concept of executive functions as an impairment in sequencing of planning and acting underlying the poorer TMT-B performance in schizophrenia patients. For this level of interpretation, the relatively large number of variables necessary to assess this feature of the performance process seems suboptimal for further investigations regarding its neurobiological correlates.

The present paper from the same study presents an exploratory attempt to develop an index summarizing the strategic problems in the TMT-B performance process and describes additional data on the state/trait specificity of these difficulties. A more detailed description of the study is given by Wölwer and Gaebel (2002).

Methods

• Subjects

Twenty-three inpatients with acute schizophrenia (S, 7 female, 16 male, mean age 30.0±9.3), 17 inpatients with acute depression (D, 11 female, 6 male, mean age 45.5±10.9) and 21 non-psychiatric controls (N, 15 female, 6 male, mean age 36.3±10.5) were assessed at least twice within four weeks, after giving written informed consent. The patients were diagnosed according to DSM-III-R (American Psychiatric Association 1987) and were tested within three days after admission (T0) and after four weeks (T1) of neuroleptic or antidepressant treatment, respectively. Mean daily neuroleptic dose in schizophrenia patients was 378 mg chlorpromazine equivalents (Wyatt 1976). Four schizophrenia patients and five depressive patients experienced their first episode, the remaining patients had a mean illness duration of 5.9 (S) and 6.4 (D) years, respectively. The three groups did not differ in educational level (years of training: S: 11.1±3.1; D: 11.5±3.7; N: 12.5±3.4) or hand preference (right-handedness: S: 91%, D: 94%, N: 90%), but as is to be expected in unselected samples, the schizophrenia sample on average was younger than the depressive sample (ANOVA F_{2,60}=11.5, p<.001) and contained fewer female patients ($\chi^2=8.5$, p=.014).

A subgroup of 14 schizophrenia patients and 14 depressives staying longer at the hospital due to their more severe illness was additionally reassessed shortly before discharge (T2), on the average six weeks after T1, in a widely remitted stage of their illness. Besides their more severe illness this subgroup showed no significant difference from the rest of the sample only assessed twice in any of the experimental measures at T0 or T1.

• Procedure

TMT-B was given in a computerized version (Reischies and Wilms 1989), requiring the subjects to connect digits alternating with letters in ascending order as quickly as possible using a cursor. The cursor position was recorded every 100 ms. Concurrently, eye movements were recorded by means of head-free infrared oculography (system DEBIC 80). Following careful individual calibration, eye position during task performance was recorded every 20 ms. Fixations were calculated offline according to the algorithm by Kliegl and Olson (1981)

with a temporo-spatial window of 200 ms x 0.5° x 0.65°.

Clinical course and extrapyramidal side effects of neuroleptic treatment were assessed using standardized rating scales (BPRS, Overall and Gorham 1962; SANS, Andreasen 1982; BRMES, Bech et al. 1979; EPS, Simpson et al. 1970; AIMS, Guy 1976).

• Data reduction

In order to grasp the complex interaction of eye and hand movements, the process of task performance was divided into periods of "planning", "acting" and "resting", respectively, determined every 500 ms by an automatic algorithm, with planning periods operationalized by non-cursor fixations, acting periods by fixations on a moving cursor, and resting periods by fixations on a non-moving cursor. To model and quantify the "strategy" of task performance behind this sequence of elementary steps, the sequential dependence of consecutive periods of planning, acting and resting was determined by calculating individual 3x3 matrices with transition probabilities. The resulting nine transition probabilities were structured using factor analysis with varimax rotation across all three groups at T0. T1- and T2-scores were estimated on the basis of the T0-factor structure, justified by quite comparable factor structure in longitudinal comparisons (similarity coefficient for factor matrices according to Gebhardt 1967: Q=0.94 for T0 vs. T1-matrix, T0 vs. T2: Q=0.92; T1 vs. T2: Q=0.91).

• Data analysis

The time to complete the task ("performance time") and factor scores at T0 and T1 were analyzed by separate 3x2-MANOVAs (group x time). As an estimate for the further course, T2-data of the smaller subsample of patients were compared with the T1-data of non-psychiatric controls by single factor ANOVA. In case of significant effects Tukey honestly significant difference tests (HSD) were used for post hoc comparisons. According to the exploratory character of the study unadjusted error probabilities of $\alpha = .05$ were used.

Results

• Clinical course

Both groups of patients showed significant clinical improvement between T0 and T1. Schizophrenia patients improved in positive symptoms (BPRS sum of subscales thought disturbance, activation and hostility, BPRS-PS: T0: 24.5±6.5, T1: 18.2±5.8; t=4.63, p<.001) and in negative symptoms (SANS-summary score: T0: 13.7±3.6, T1: 9.5±5.8; t=3.84, p=.001), whereas depressive patients improved in depressive symptoms (BRMES sum score: T0:

20.6±4.6, T1: 13.0±6.1; $t=6.21$, $p<.001$) and negative symptoms (SANS-summary score: T0: 14.0±3.0, T1: 9.0±5.4; $t=3.13$, $p=.007$). The subgroups reassessed at T2 had initially at T0 more severe symptoms than the rest of the samples, but showed further clinical improvement between T1 and T2 (BPRS-PS in S at T2: 15.7±4.9; T2 vs. T1: $t=2.22$, $p=.045$; BRMES-sum in D at T2: 3.5±2.1; $t=7.79$, $p<.001$).

• Performance time

Besides their significantly poorer performance in the T0-T1 interval (Wölwer and Gaebel 2002), the present additional analysis of the T2-data revealed that schizophrenia patients (S) at discharge still demonstrated a trend to poorer performance compared with non-psychiatric controls (N) at T1 (ANOVA: $F_{2,46}=2.48$, $p=.09$; HSD S vs. N: $p=.06$). Though depressive patients also performed worse than non-psychiatric controls in the T0-T1 interval, their performance improved in the T1-T2 interval with no significant difference remaining compared to controls.

• Performance strategy

The principal component analysis revealed three factors with eigenvalues greater than 1 as independent dimensions of performance strategy. These three factors accounted for 77% of the variance (Table 1). The first factor represented the probability of resting periods in the performance process ("resting factor"). The second factor more closely represented planning strategy, i.e. primarily the interaction and fluent alternation between planning and acting periods ("visuo-manumotor integration factor"). To a lesser extent a low probability of starting acting periods from a resting state contributed to this bipolar factor. The third factor also was bipolar with the length of acting and planning sequences at opposite ends of a continuum ("sequence length factor"), representing the bias towards a performance strategy dominated either by persisting acting (with short planning) or by persisting planning (with short acting) periods.

Group differences could only be shown for the "visuo-manumotor integration factor"; due to significant correlations with age within each group, age was used as a covariate in the analysis of this factor. Besides a significant main effect "time of testing" ($F_{1,58}=5.19$, $p=.026$) indicating an increase in factor scores from T0 to T1 independent of group, a highly significant main effect "group" ($F_{2,58}=7.37$, $p=.001$) followed by HSD revealed significantly lower factor scores in schizophrenia patients than in non-psychiatric controls in the T0-T1 interval (Figure 1; HSD S vs N: $p=.001$). Analysis of T2 data proved the persistence of this difference (ANOVA: $F_{2,46}=9.4$, $p=.0004$; HSD S vs. N: $p<.001$), i.e. schizophrenia patients showed less frequent

planning-acting alternations than controls in TMT-B performance during their whole hospital stay. Depressive patients differed neither from schizophrenia patients nor from controls in the T0-T1-interval, but then improved up to the level of controls before discharge, resulting in a significant difference between depressive and schizophrenia patients at T2 (HSD: S vs. D: $p=.006$).

Table 1

Factor loadings, eigenvalues and explained variance resulting from a factor analysis on transition probabilities between "planning", "acting", and "resting" periods at T0 (factor loadings > .50 are framed)

	Factor 1 "Resting"	Factor 2 "Visuo- manumotor integration"	Factor 3 "Sequence length"
Eigenvalue	3.43	1.91	1.58
Explained variance	38.2%	21.2%	17.6%
Transition probability			
resting - planning	.89	-.03	.23
planning - resting	.79	-.12	-.04
resting - resting	.68	-.19	-.14
acting - resting	.74	-.21	.44
planning - acting	-.04	.97	.07
acting - planning	-.34	.89	-.02
resting - acting	.17	-.53	.38
acting - acting	-.15	-.34	.85
planning - planning	-.25	-.31	-.90

"Visuo-manumotor integration" was also the only factor which showed a significant correlation with performance time across groups (T0: $r=-.60$, T1: $r=-.62$, T2: $r=-.52$ for age corrected scores, respectively), indicating that good TMT-B performance was related to frequent alternations between visually searching and manually connecting targets without or only with few pauses.

Intervening variables

A stepwise multiple regression analyses using age-corrected "visuo-manumotor integration" as criterion and demographic (sex, education), anamnestic (illness duration), psychopathological (BPRS- and SANS-sumscores), motor (EPS-, AIMS-sumscores) and medication characteristics (mean daily neuroleptic dose) as potential predictors revealed neither at T0 nor at T1 a significant and consistent relationship. Confirming results could be obtained using additional univariate comparisons: in schizophrenia patients neither a comparison of patients premedicated with neuroleptics within the last six weeks before admission ($n=14$) vs. those not premedicated

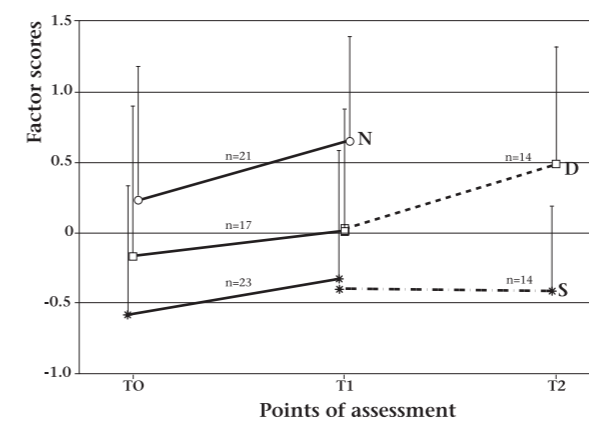


Figure 1

"Visuo-manumotor integration" factor scores (corrected for age) in patients with schizophrenia (S) and depression (D) at admission to the hospital (T0), four weeks later (T1) and at discharge (T2) as well as in non-psychiatric controls (N) assessed twice four weeks apart (T0, T1)

($n=9$) nor a comparison of patients medicated on the day of T0 assessment before the testing session ($n=13$) vs. schizophrenics unmedicated at T0 ($n=10$) showed an influence on performance time or measures of the performance process at T0 (2x2-ANOVA premedication x T0-medication). Also gender differences emerged only in an inconsistent manner (female subjects performed poorer at T0, but not at T1 and scored higher on the resting and sequence length factors at T1 but not at T0).

In order to investigate the possible effect of the existing age difference between groups, the analyses of the factor scores were repeated in smaller subsamples restricted to an identical age range (i.e. $n=13$ controls, $n=11$ schizophrenia patients and $n=11$ depressive patients with an age range of 28 to 51 years). This analysis verified the results in principle, though with minor variations in size effect.

Discussion

Based on the interaction of eye and hand movements a comprehensive index summarizing schizophrenia patients' strategic difficulties during the performance process in TMT-B was developed. This "visuo-manumotor integration factor" describes the fluent alternation between planning and acting periods within the performance process. Its significant correlation with performance time indicates frequent alternations between these two states to be a prerequisite for good TMT-B performance. Since none of the other factors showed any relevance, the impairment in TMT-

B performance often reported in schizophrenia patients seems to be primarily the result of insufficient sequencing of planning and acting, i.e. the interaction between visually searching and manually connecting targets seems to be less efficient in schizophrenia patients compared to non-psychiatric controls. None of the various univariate and multivariate analyses performed revealed a consistent effect of the intervening variables investigated (gender, education, illness duration, clinical status, medication). Furthermore, no hint could be found that the different age ranges typical for depression and schizophrenia may have distorted group differences. Thus, insufficient sequencing of planning and acting in schizophrenia seems not to be merely the result of moderator variables.

Although such analyses of the TMT performance process to our knowledge have not been accomplished by other investigators yet, the fact of inefficient performance strategies or problem solving strategies in schizophrenia patients has also been reported previously (e.g. Morice and Delahunty 1996; Morris et al. 1995; Pantelis et al. 1997). It is generally hypothesized that such results are due to a lack of connectivity between circuits associated with prefrontal cortical areas. Each of the prefronto-striato-thalamic pathways described by Alexander et al. (1986) seems related to a specific pattern of cognition and behaviour (Cummings 1993). Accordingly, a dysfunction of the circuit involving the dorsolateral prefrontal cortex is associated with deficits in executive functions and motor programming, resulting in impairments in temporal and sensory integration, planning and maintenance of goal-directed behaviour (Pantelis and Brewer 1995). Recently, functional imaging studies have proved and further differentiated the role of these circuits in planning (Baker et al. 1996; Owen et al. 1996; Koechlin et al. 1999, 2000; Fincham 2002). An impairment in "spatio-temporal segmentation" (Daigheault et al. 1992) or "temporal structuring of behaviour" (Fuster 1999) seems to match the present results best. In the broader sense of "planning" used in these prefrontal lobe models - comprising the whole process of behaviour structuring instead of the narrow definition of "visual searching" in the present study - the deficit in TMT-B performance seems to be based on an insufficient planning strategy. Placed in the model of "cognitive dysmetria" (Andreasen et al. 1998) as an integrative concept of schizophrenia patients' cognitive dysfunctions, these deviances can be taken as a behavioural indicator of the difficulties in the coordination and the prioritization of information processing which characterize cognitive dysmetria. In extension of the prefrontal lobe models, cognitive dysmetria is believed to originate from a

disruption in a parallel distributed and dynamic circuitry among prefrontal regions, thalamic nuclei and, additionally, the cerebellum.

The results obtained in the present study resemble the conclusions drawn from our first analyses based on a whole pattern of results in a number of variables (Wölwer and Gaebel 2002) and summarize most of this information on deviances in the performance *process* (as opposed to performance time as a summarizing index of the performance *result*) in only one index. This could be an easy and valid starting point for further investigating brain-behaviour relationships. The additional T2 assessment included not only proved the trait characteristic of these difficulties in schizophrenia, but also hint at a certain nosological specificity, if illness course is taken into account: insufficient "visuo-manumotor integration" at discharge occurred exclusively in schizophrenia patients. As far as depressive patients' performance and planning strategy deviates from controls at all, this only seems to be a state dependent effect as opposed to the more trait-like deficits shown by schizophrenia patients throughout their hospital stay.

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Neuroimaging Community between Schizophrenia and Obsessive Compulsive Disorder: A Putative Basis for Schizo-Obsessive Disorder?

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Summary

Four major brain regions have been repeatedly implicated in the pathophysiology of obsessive compulsive disorder (OCD) in *in vivo* neuroimaging studies: the caudate nucleus, the orbitofrontal cortex, the anterior cingulate gyrus and the mediodorsal thalamic nucleus. The present review describes the neuroimaging studies on schizophrenia, pertaining to these brain regions. Our working hypothesis is that such common brain regions, if dysfunctional in schizophrenic patients, would be candidates for a neural network subserving the newly emerging syndrome of schizo-obsessive disorder. Findings, though, are controversial. We conclude that further studies, aimed at specific monitoring of these brain regions, in patients suffering from the schizo-obsessive syndrome are warranted.

Key words: obsessive compulsive disorder, schizophrenia, caudate nucleus, orbitofrontal cortex, cingulate gyrus, mediodorsal nucleus.

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Acknowledgement

This work was supported by the Sarah and Moshe Mayer Foundation for research (Tel-Aviv and Geneva).

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Introduction

The last decade has witnessed a surge of reports dealing with the comorbidity of obsessive compulsive disorder (OCD) and schizophrenia (Berman et al. 1995; Eisen et al. 1997; Lewis et al. 1991; Kozak and Foa 1994). Whereas the prevalence of OCD in the general population is about 2% (Weissman et al. 1994), the prevalence of OCD among schizophrenic patients is 7-25% (Eisen et al. 1997; Berman et al. 1995). It seems, therefore, that schizo-phrenia predisposes the patient to manifestations of OCD by a mechanism which remains to be clarified. This over-representation of OCD in schizophrenic patients has coined the term "schizo-obsessive" (Eisen et al. 1997; Berman et al. 1995).

A plethora of *in vivo* and *in vitro* neuroimaging studies have implicated a large number of neuroanatomical and functional defects in schizophrenia, reflecting both the complicated nature of this disorder and the large variability in its behavioural manifestations. In parallel a surge in neuroimaging studies in OCD has led to the formulation of a putative "OCD neural network" (Insel 1992).

In the present review we will evaluate the overlap between schizophrenia and OCD putative neural networks in an attempt to identify candidates for common neurobiological substrate that could be involved in the schizo-obsessive disorder.

Obsessive compulsive disorder

• The OCD neural network

Though discrepancies between the studies on OCD exist, it is possible to extract from these studies a putative "OCD neural network" which is by and large consistent across all reports.

The most documented region in neuroimaging/regional cerebral blood flow studies in OCD is the caudate nucleus. Increase in cerebral blood flow in this area of the brain

have been visualized under both resting conditions (Lucey et al. 1995, 1997a, 1997b; Rubin et al. 1995; Baxter et al. 1987) and following provocation of OC symptoms by a variety of pharmacological and behavioural challenges (Hott Pian 1998; Cottraux 1996; McGuire et al. 1994; Rauch et al. 1994). These functional abnormalities were found to be without structural correlates (Aylward et al. 1996; Jenike et al. 1996). Structurally, Robinson et al. (1995) found no alterations in prefrontal cortical volume while others (Jenike et al. 1996; Szesko 1998) showed alterations in specific prefrontal regions such as the orbitofrontal cortex.

In order of frequency, the next brain region in which changes in activity occur is the orbitofrontal cortex. All studies implicating this region have used the paradigm of brain activation via either symptom provocation (Rauch et al. 1994, 1997; McGuire et al. 1994; Breiter et al. 1996) or neutral stimulation (Cottraux et al. 1996).

The cingulate gyrus was also found to be activated, as assessed by imaging studies, in OCD patients by some researchers (McGuire et al. 1994; Rauch et al. 1994) as were portions of the temporal cortex (Breiter et al. 1996; Zohar et al. 1989; Cottraux et al. 1996; Lucey et al. 1995) and the thalamus (Hott Pian et al. 1998; Cottraux et al. 1996; Lucey et al. 1995; McGuire et al. 1994; Rauch et al. 1994; Rubin et al. 1992).

These findings obtained by various methods of functional *in vivo* neuroimaging are corroborated by lesion studies. Lesions of the caudate nucleus have been shown to precipitate OCD-like behaviour patterns and resection of the anterior capsulae, which disconnects the orbitofrontal cortex from the basal ganglia, has been shown to relieve OCD symptoms. In addition, it seems that OCD is frequently manifested in Tourette's syndrome patients, another disorder in which the basal ganglia were implicated (Wolf et al. 1996).

Structural studies have yielded non-uniform results. The caudate nucleus of OCD patients was reported to be both smaller (Luxenberg et al. 1988; Robinson et al. 1995; Rosenberg et al. 1997) and larger (Scarone et al. 1992) than that of healthy controls. Gilbert et al. (2000) found increased volume of the thalamus in OCD, which was affected (decreased) by monotherapy with SSRIs.

Decreased metabolic rates were reported in whole cortex and in lateral prefrontal cortex in OCD patients (Martinot et al. 1990).

In the following sections we will describe the presence of OCD-associated structural and

functional alterations in schizophrenia. The most consistent findings are summarized in Table 1.

Table 1

Summary of structural and activity neuroimaging studies in OCD and schizophrenia

Brain Region	Activation Studies		Structural Studies	
	OCD	Schizophrenia	OCD	Schizophrenia
Caudate nucleus	≠	≠∅	≠∅	≠∅
Orbitofrontal cortex	≠	≠	no data	≠∅
Anterior cingulate gyrus	≠	≠∅	no data	∅
Mediodorsal thalamic nucleus	≠	∅	no data	no data

Table presents pertinent findings related to the OCD "neural network".

≠ increased activation or volume

∅ decreased activation or volume

OCD obsessive compulsive disorder

Schizophrenia

As shown in Table 1 there is a partial overlap of findings between OCD and schizophrenia in the caudate nucleus and anterior cingulate gyrus. No overlap was found in thalamic structures. It is noteworthy that a study focusing on regional metabolic rates of glucose, using PET, in OCD, schizophrenia and major depression has demonstrated that the cerebral functional connectivity appeared differentially changed in these disorders suggesting different impairment (Mallet et al. 1998).

• Abnormalities in the caudate nucleus in schizophrenia

As the caudate nucleus is the main target of the nigro-striatal dopaminergic pathway and one of the major neurochemical hypotheses in schizophrenia is the dopamine hypothesis, it is not surprising that a substantial proportion of imaging studies have focused on the caudate nucleus. Results of structural studies on the volume of the caudate nucleus are controversial with some finding enlarged volumes in schizophrenic patients (Swayze et al. 1992; Breier et al. 1992; Elkashef et al. 1994; Chakos et al. 1994; Hokama et al. 1995; Frazier et al. 1996a, 1996b). While others found decreased volumes of this structure in schizophrenia (Keshavan et al. 1998; Shihabuddin et al. 1998; Stratta et al. 1997) yet others found no differences in the size of striatal structures in this disorder (DeLisi et al. 1997). A recent study found increased basal ganglia volume in schizophrenia patients treated with typical neuroleptics over a period of two years, as well as decreased volume of these structures in patients treated for the same length of time with atypical neuroleptics (Corson et al. 1999). This structural imaging study lends some corroboration to the notion that basal ganglia

structures are decreased in drug naive schizophrenic patients. Functional studies have reported altered regional cerebral blood flow in this region. Again, results are inconclusive and findings contradictory, with some groups reporting increased rCBF in the caudate of schizophrenic patients (e.g. O'Connell et al. 1989) and others finding decreased rCBF (Vita et al. 1995).

• Abnormalities in the orbitofrontal cortex in schizophrenia

As traditionally the dorsolateral prefrontal cortex was implicated in the pathophysiology of schizophrenia the documentation of the structure and function of the orbitofrontal cortex in this disease is scarce. *In vivo* it was reported that this region is active during auditory hallucinations (Silbersweig et al. 1995). Structural (Senitz and Winkelman 1981) and neurochemical (Meador-Woodruff et al. 1997) abnormalities in this cortical region were also reported in *in vitro* postmortem studies. *In vivo* studies have reported both increased volume of the orbitofrontal cortex (Szesko et al. 1999) in schizophrenia as compared to healthy controls, and decreased volume (Goldstein et al. 1999).

• Abnormalities in the anterior cingulate in schizophrenia

In analogy to the striatal findings, findings regarding the anterior cingulate gyrus have also been controversial. A number of studies reported decreased activation of this area in schizophrenia (Andreasen et al. 1992; Siegel et al. 1993; Haznedar et al. 1997; Carter et al. 1997) while others reported increased activation (Catafau et al. 1994; Andreasen et al. 1997; Kishimoto et al. 1998). Reports on structural abnormalities of the cingulate gyrus are equally non-conclusive. Decreased volume of this structure (Noga et al. 1995), decreased gray matter (Ohnuma et al. 1997) and no change relative to healthy controls (Nordhal et al. 1996) were reported. In addition, a number of studies by the same group have focused on the delusional aspect of schizophrenia and reported decreased perfusion in this area to be correlated with presence of delusions (Erkwoh et al. 1997; Sabri et al. 1997a, 1997b).

• Abnormalities in the mediodorsal thalamic nucleus in schizophrenia

Even though the mediodorsal thalamic nucleus is involved in the thalamus-striatum-prefrontal cortex circuitry, which supposedly underlies the schizophrenic symptomatology, this region has scarcely been studied directly. Two reports, both *in vitro* postmortem studies, have found a reduction in the number of neuronal and glial cells in this structure in both medicated and drug-naive schizophrenic patients (Pakkenberg 1990, 1992). A recent functional study has reported significantly decreased activity in the

mediodorsal thalamic nucleus of schizophrenic patients as compared to both healthy controls and schizotypal personality disorder (Hazlett et al. 1999).

It seems that of all areas reviewed above, the caudate nucleus is one of the best candidates for explaining the susceptibility of schizophrenic patients to OCD. The evidence of its reduced volume in schizophrenia seems to be corroborated by the precipitation of OC symptoms by lesions to this structure in non-schizophrenic OCD patients. Unfortunately this region has not been monitored by *in vivo* neuroimaging methods in patients suffering from both schizophrenia and OCD (Levine et al. 1998). Even if this hypothesis is correct it is to be surmised that caudate lesions will turn out to be a necessary but not sufficient prerequisite for the expression of OCD in schizophrenia.

Conclusion

Though, as we have shown, there are some functional and structural similarities between the neuroanatomical regions implicated in OCD and schizophrenia, there is no single work in schizophrenia where all OCD-related regions are detected to be malfunctioning as a network. It is possible, therefore, that the OCD symptomatology seen in some schizophrenic patients is unique and not necessarily subserved by the same neural network which subserves non-schizophrenic OCD. Furthermore, it is also possible that since, on the whole, schizophrenia is characterized by hypoactivation, possibly secondary to cell loss, of some of the putative "schizophrenic neural network", while OCD is on the whole characterized by hyperactivation of its own neural network, the functional changes in the subgroup of schizophrenic patients suffering from OCD are expected to be much too subtle to be detected. As neuroanatomically the only regions which do not overlap in the two disorders are prefrontal cortical regions (orbitofrontal in OCD vs. dorsolateral in schizophrenia), it may be reasonable to focus future brain imaging efforts in schizo-obsessive patients on these regions. However, the "communality" between schizophrenia and OCD may also be viewed as representing the non-specific nature of neuroanatomical alterations across a variety of psychiatric disorders, including schizophrenia and OCD.

Even though a number of studies have shown that the prevalence of OCD in schizophrenic patients is approximately ten-fold higher than the expected value, only one brain imaging study was dedicated to such patients (Levine et al. 1998). Findings of this preliminary study indicate that in the subgroup of schizophrenic patients who are mildly affected by OCD there

is a negative correlation between dorsolateral prefrontal cortex activation and severity of OC symptoms. Unfortunately this study has not assessed activation in other areas supposedly subserving the OCD syndrome.

Further large scale studies specifically evaluating schizophrenic patients with OCD are required before any definite conclusions can be drawn. Such studies should, if undertaken, compare the structure and activity of all structures related to OCD in the three relevant groups of mental disorders: schizophrenia, OCD without and with schizophrenia. The specific brain regions that should be assessed seem to be at present the orbitofrontal cortex and the basal ganglia.

Finally, as demonstrated in Table 1, the apparent controversy of some of the findings in schizophrenia may indicate the existence of two phenotypes: schizophrenic patients with and without concomitant OCD. Those with similar brain imaging results to non-schizophrenic OCD could be schizo-obsessive patients. Schizophrenia with OCD symptoms might have unique neuroanatomical and functional alterations, which might be more common with OCD than with schizophrenia without OCD.

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Dementia Paralytica (Neurosyphilis): A Clinical Case Study

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Summary

This study reminds clinicians that syphilis presents in many guises. Wars, migration and sexual promiscuity prepare the ground for its return as an important cause of neurological and psychiatric syndromes. Our patient's diagnosis was not suspected at earlier admission. Stage III spirochaetosis was improved by high dose penicillin.

Key words: syphilis, genital ulcers, exanthemata, Argyll-Robertson pupils, penicillin.

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Introduction

Syphilis was almost eradicated as a disease in numerous European countries. However, increased incidence of the disease was recorded in Russia, Baltic countries and Norway. It is quite possible that the incidence is also increased in the countries of the former Yugoslavia because of increased risk factors in these regions during and after war: migrations, poverty, different armies, prostitution, substance abuse, etc. It is hard to obtain precise epidemiological data mostly due to the failure to recognize the disease (or misdiagnosis) in its early and late stages. Early diagnosis of syphilis is essential since the disease is curable when recognized in its stages I or II. The complexity of the diagnosis of the disease in its advanced stages (and unfortunately poorer outcome) will be illustrated by the case report of a patient affected by central nervous system syphilis, i.e., neurosyphilis (paralytic dementia, progressive paralysis).

Syphilis and neurosyphilis

It is rather difficult to obtain precise epidemiological data on the disease mostly because, in our opinion, of insufficient knowledge about syphilis and incorrect diagnosis in early and advanced stages of the disease. The trend towards an inadequate phenomenological diagnosis of "primary" degenerative "dementia of Alzheimer's type" (which is a histopathological category) without trying to detect any other causes of dementia, is an example of the increasingly frequent non-aetiological (consequential) approach in modern medicine, which makes the precise clinical diagnosis and aetiological treatment difficult, particularly in the so-called "systemic" and "autoimmune" diseases (some of them are infective diseases: streptococcus and other bacterial diseases, lues (syphilis), tuberculosis, Lyme, etc.).

Syphilis is a systemic disease and may affect practically all organs and systems, but is curable if recognized in its early stages (I and II). Early diagnosis is essential in general practice, dermatovenereology, gynaecology, urology, rheumatology, immunology, allergology, orthopaedic surgery and oncology. Adequate antibiotic treatment of the initial stages of lues may enable avoidance of CNS complications (paralysis progressiva or dementia paralytica,

tabes dorsalis, pseudotumor cerebri) and other multisystemic complications of syphilis (cardiovascular, musculoskeletal, ocular, cutaneous, hepatic, renal, pancreatic, etc.) encountered from years 5-15 after initial inoculation.

Case report

The complexity of the diagnosis of neurosyphilis (neurosyphilis) will be illustrated by this case report on a patient with dementia paralytica (paralysis progressiva) treated at the Department of Organic Mental Disorders of the Institute of Psychiatry and Institute of Neurology, University Clinical Centre, Belgrade.

The patient, S.S., born on 5 July 1949, was admitted to our department on 11 November 2000 with a referral diagnosis of suspected psycho-organic syndrome. It was his third hospitalization. The patient was initially treated at the Institute of Mental Health in Belgrade from August till October 2000, as well as the Department of Neuropsychiatry of the General Hospital in his hometown (October-November, of the same year) from where the patient was referred to our institution for further diagnosis and treatment.

The first clinical impression was: delirium and neuroleptic syndrome, or dementia with delirium and neuroleptic syndrome. Major complaints on admission included rigidity, speech difficulties, perceptible, dysgnostic and dysmnesic disorders, disorientation, aggressive attacks, insomnia, sweating, headache, nightmares and urinary retention.

Evaluation of the medical records revealed that initial behavioural (personality) changes characterized by occasional disorientation, amnesic episodes, affective lability and aggressiveness developed by the end of 1999 and were preceded by intensive alcohol abuse lasting several months. Based on the different information obtained from the family, the patient consumed alcohol every day for more than 30 years, and since February 2000, he was frequently drunk and became both verbally and physically aggressive. During the same August, his family persuaded him to consult a psychiatrist, after physical assault of a police officer which happened when the patient was drunk. At the time, the patient was initially hospitalized at the Institute of Mental Health in Belgrade, diagnosed as mixed psychotic disorder caused by alcohol abuse (F 10.56) and treated by the neuroleptic drug haloperidol by injection. EEG examinations performed on the same occasion evidenced frontal bilateral slow theta and delta waves. The treatment was continued at the neuropsychiatric department in his hometown, but he developed neuroleptic

syndrome. Since favourable therapeutic effects were not achieved, the patient was referred to our institution.

As for the personal history of the patient, it is to be mentioned that the patient was born the second of three children in a farmer's family. His psychomotor development was uneventful, free of stigmata during childhood and adolescence. He completed his elementary school and two years of the catering school with high honours as well as exemplary military service. He married at the age of 17 a girl two years younger. He has been married for 34 years and fathered three healthy children. His career progressed from being a waiter to now owning his own restaurant. During his life he had frequent extramarital intercourse with the opposite sex, with foreign citizens, particularly with women from Romania and Bulgaria. His health was good till 1992 when he was admitted to the Institute of Rheumatology in Belgrade because of skin rash, mouth and genital ulceration, palmar and plantar skin changes, pain and redness of the right eye, weight loss, malaise and joint pains. During hospitalization, aphthous oral ulcers, genital ulceration with balanitis, serofibrous iridocyclitis and skin exanthema, predominantly palmar and plantar were identified and recognized as "Behçets syndrome" (which, based on the clinical picture, corresponded to the stage II of spirochetosis). The patient was treated by low dose glucocorticoid with local ophthalmological therapy, which had only minor effects on the skin lesions, and was completely ineffective for oral ulceration and iridocyclitis. Only after the introduction of erythromycin did all skin and mucosal changes subside. Neither serological nor other aetiologically directed investigations were performed.

Family history of the patient was characterized by the suicide of his mother from ingestion of caustic soda at the age of 50. The patient's father, a chronic alcoholic for years, died in his sixth decade with advanced dementia; his older sister was a psychiatric patient without more specific data on the type of disorder and treatment.

Upon admission to the department, the patient's psychological condition demonstrated poor attention span, diffuse memory deficit, dysphoric mood and loss of appetite. Neurological examination showed right anisocoria, dysphasia, dysarthria, rigor of the cervical muscles, enhanced tone of the upper extremities of extrapyramidal type, symmetrical and right action tremor, enhanced tone of the lower extremities of extrapyramidal type and myotatic reflexes symmetrically reduced.

Treatment was initiated by detoxification

leading to resolution of the extrapyramidal symptoms. After a few days, the discontinuation of alcohol led to the development of subdelirious (asptinential) crisis, which was resolved by clomethiasole and low doses of haloperidol. In the course of further treatment, the clinical picture was dominantly characterized by intellectual-memory deficit of cortical type with occasional fluctuating findings of disinhibiting phenomena, left hemiparesis and dysarthria with dysphasia.

Such diverse and unstable findings led us to consider other differential diagnostic aspects (vascular pathology: CVI, MID; Alzheimer's type dementia; alcoholic dementia with delirium; endocrine (thyroid) and/or metabolic imbalance?) For the purpose of more precise diagnosis, additional tests, presented in Table 1, were conducted.

Table 1

Additional tests and their results

Brain NMR: moderately prominent cortical and subcortical reductive changes (dominantly prefrontal and frontal)

Colour duplex scan of the cervical and brain main arteries: in the proximal part of the left internal carotid artery fibrous non-ulcerated plaque with 5% narrowing. At the same time, clearly demarcated node in the left thyroid lobe with mildly enhanced perinodal vascularization is recorded.

Biochemical analysis of the blood and urine - within physiological values

Transcranial colour Doppler of the Circle of Willis arteries: absence of haemodynamically significant morphological changes

EEG: completely irregular, significantly disorganized in the course of hyperventilation recording the picture of irregular slow polyrrhythmia bi-fronto-temporally

Endocrinology findings: sonographic examination of the thyroid gland showed adenomatous node with minor regressive changes in the left lobe up to 22 mm in diameter. T4 within normal range.

The clinical picture was characterized by the presence of anisocoria, Argyll-Robertson pupils, pyramidal (left hemiparesis) and extrapyramidal motor disorders, dysarthria as well as NMR findings (dominant frontal atrophy), EEG findings (bi-fronto-temporal dysfunction and electric activity disorganization), along with the history of behavioural disorders and personality changes as well as intellectual/memory deterioration and other findings highly suspicious of stage II syphilis: iridocyclitis and skin exanthema, predominantly palmar and plantar (in the course of treatment at the Institute of Rheumatology), led us to perform further examinations including serological tests

intended for detection of *Treponema pallidum*. This somewhat forgotten spirochaetosis was confirmed by V.D.R.L. test which showed a positive blood titre at the H1:128 level. These findings, along with the described clinical picture, the basis for establishing the diagnosis of neurosyphilis, i.e., stage III spirochaetosis.

For the purpose of CSF examination and further therapy, the patient was referred to the Institute of Neurology in Belgrade. *T. pallidum* CSF titre level positively indicated neurosyphilis. Treatment with high dose penicillin was initiated which led to better organization of his behaviour and a certain improvement of cognitive function. The patient was discharged in relatively stable condition with prognostically ambiguous outcome.

Interestingly, the patient's spouse was at the same time treated at the Institute of Rheumatology for onset of the exanthem recognized as lupus erythematosus. The disorder was "diagnosed" using HLA cell typing although LE cells were not found in the blood. She was initially treated by high doses of corticosteroid, followed by cytostatic therapy (!?), which showed no effect on the skin changes and produced at the same time major adverse effects. After diagnosis of neurosyphilis in our patient, *T. pallidum* serological tests were performed on his spouse, and its presence confirmed. Since the disease was in its stage II, antibiotic therapy was applied and the prognosis was considered favourable.

Conclusion of case study

Our patient was alcoholic for years (symptomatic alcohol abuse), with personality disorders (disinhibition, aggressive acting-out, frequent sexual contacts, etc.) and positive psychiatric family history. At the age of 43 he was treated for skin rash (predominantly palmar and plantar, indicative of lues!), oral and genital mucosal ulceration and iridocyclitis, interpreted as "Behçets syndrome". The progressive psychological changes developed at the age of 50 and were characterized by the affective and psychopathic (pseudo-psychopathic) symptoms along with cognitive and memory disturbances. In the course of treatment, the patient developed disorders of consciousness, i.e., delirium, and thereafter the clinical picture became predominantly characterized by dementia syndrome (cortical type) with diverse and changeable neurological defects. Since toxic, traumatic, vascular, endocrine, metabolic and other causes of the disorder were ruled out, the investigations were directed toward infectious aetiology, which was confirmed by lues-specific serological test.

Final conclusions and recommendations

Diagnosis of neurosyphilis and paralytic dementia may be difficult for several reasons:

1. Physicians consider the disease to be infrequent (in spite of "sexual revolution", wars, migrations, prostitution, increase of addiction diseases!);
2. The disease may mimic a large number of other somatic and mental disorders during all three stages;
3. Antibiotic therapy prescribed because of other diseases may neutralize the serological tests for lues and alter the clinical pictures;
4. New clinical forms may develop (the so-called "formes frustes");
5. Frequent clinical pictures include: neurasthenic conditions, personality and behaviour disorders, i.e. alterations, particularly from the ethical point of view; depressions and confusions; hypomanic and manic conditions, paranoid and schizophreniform conditions, amnesic disorders; secondary alcohol and drugs abuse is frequent; deliriums; TIA; "transitory" and also recurrent neurological signs affecting the eyes – anisocoria, Argyll-Robertson pupils, optic nerve atrophy; speech disorders – dysarthria, dysphasia; dysgraphia, motor deficits–repeated and "transitory" (hemi, para, mono) paresis, sensitivity disorders, gait disorders, epileptic and epileptiform fits, lancinating pains, focal and global dementia; affection of numerous organs i.e., (multi)systemic affection;
6. Serological diagnostic procedures are infrequently and/or inadequately performed (paradoxical conclusions based on the so-called "false syphilis-positive serological tests", without control test: TPHA, FTA-ABS, Elisa), introduction of the "new" entities/illnesses such as "antiphospholipid syndrome" ("APL")!?, "systemic vasculitis of unknown aetiology", "Alzheimer's dementia with motor deficits of the paraparesis type or paraplegia", etc.);
7. Education of psychiatrists and other specialists (cardiologist, rheumatologist, oncologist, urologist, gynaecologist, surgeon, immunologist, etc.) about multisystemic and multiphasic nature of lues (as well as neuroborreliosis, tuberculosis) is frequently insufficient;
8. Unfortunately, modern medicine is not primarily directed toward aetiological, but rather toward syndromological diagnosis. The diagnostic is not aetiological: unfortunately it is more consequential (immunology, image, histopathology, etc). It results in non-causal, symptomatic treatment in disorders with known aetiology, too, as in the case of our patient and his spouse.

9. Traditional general screening for syphilis at psychiatric, neurological and geriatric departments may not always be necessary but it should be kept in mind that the disease is not rare and that early serological tests enable early diagnosis of one of only a few curable (neuro)psychiatric diseases.
10. All genital ulcers should be considered syphilitic until proved otherwise!

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ECT in the Management of Major Depression: Implications of Recent Research**Chittaranjan Andrade**

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Recent issues of the World Journal of Biological Psychiatry have carried treatment guidelines for depressive illness (Bauer et al. 2002a, 2002b). Both guidelines, however, inadequately reference recent research on the role of electroconvulsive therapy (ECT) in the management of a major depressive episode, especially when psychotic features are present. A consideration of this research should encourage the earlier use of ECT in treatment algorithms, saving the depressed patient needless suffering during less effective drug trials. We provide a brief update on this research.

1. How does ECT compare with antidepressant drugs? Response to antidepressant drugs is commonly defined as a 50% attenuation of depression ratings at the end of six weeks; it is common experience that such response is attained by no more than 70% of patients in antidepressant drug trials. In contrast, the remission rate can be as high as 87% in patients who complete a course of bilateral ECT administered at a dose that is 1.5 times the seizure threshold (Petrides et al. 2001). Of further interest, Husain et al. (Submitted) found that 10% of the patients who remitted did so with three ECT, 40% with six ECT, and 60% with nine ECT; that is, within 1, 2 and 3 weeks of treatment, respectively. Other investigators who specifically examined the speed of response to ECT also reported that depressed patients respond rapidly to the treatment, and that substantial response in most patients is obtained within two weeks (Barton et al. 1973; Segman et

al. 1995). This speed of remission is far greater than that observed in antidepressant drug trials. Sadly, no adequately-powered trials have been conducted to contrast the response and remission rates with antidepressant drugs and ECT.

2. The four-hospital Consortium for Research in ECT (CORE) administered bilateral ECT at 1.5 times the seizure threshold to patients with unipolar major depressive disorder. Patients with psychotic depression responded faster to ECT than those with nonpsychotic depression. The remission rate was slightly but significantly higher in psychotic than in nonpsychotic depressives (95% vs 83%, respectively; Petrides et al. 2001). The remission rates for patients aged 65 years and more, those aged 46-64 years, and those aged 45 years and less were 90%, 89.8% and 70%, respectively; older patients were significantly more likely to remit with ECT (O'Connor et al. 2001). A limitation of the CORE data is that they were uncontrolled; a strength is that they were obtained from a large sample (n=253) and are therefore likely to be robust. The CORE findings suggest that bilateral, 50% suprathreshold ECT is an impressively effective treatment for patients with unipolar major depressive disorder, especially for those who are older and those with psychotic depression.
3. The CORE investigators (Kellner et al. Submitted) also reported that ECT had a marked therapeutic effect on the symptom of suicidality as assessed using item 3 on the Hamilton Rating Scale for Depression. In this study, 235 of 405 patients scored 2 or more on the HRSD suicidality item. In these 235 patients, the cumulative probability of complete relief from suicidality (HRSD item 3 score = 0) was 34% after one ECT, 68% after three ECT, and 87% after six ECT. And, 95% of the patients with suicidality were free of suicidal thoughts by the end of the ECT course (Kellner et al. submitted).
4. Depressed patients may relapse despite best efforts with maintenance medications. Although there are no double-blind, controlled trials, a large body of case reports and open studies indicates that continuation and maintenance ECT improve the long-term course and outcome in such patients (Gagne et al. 2000; Andrade and Kurinji 2002) with little burden of adverse effects (Barnes et al. 1997; Datto et al. 2001). Continuation and maintenance ECT should therefore be included as an important resource in patients who relapse despite pharmacotherapy, and in those who do not tolerate maintenance pharmacotherapy.
5. Much research has addressed and is addressing technical aspects of ECT such as electrical dosing with right unilateral ECT, composition of the electrical stimulus, spacing of ECT treatments,

and other matters. While right unilateral ECT spares cognitive functions relative to bilateral ECT, the precise dose at which it is therapeutically equivalent to but cognitively less toxic than 50% suprathreshold bilateral ECT remains to be defined (Sackeim et al. 1987, 1993, 2000; McCall et al. 2002). Until definitive results are obtained, the gold standard is probably bilateral ECT administered thrice weekly at a dose that is 1.5 times the initial seizure threshold (Petrides et al. 2001). These technical issues should be kept in mind when interpreting research on ECT, and when practising ECT.

Overall, the findings of the cited studies strongly recommend that 50% suprathreshold, bilateral ECT should be prescribed earlier rather than later in a treatment algorithm in order to reduce patient suffering and return patients sooner to a functional state. This recommendation is especially applicable to patients who are older, psychotic or suicidal. It may even be useful to consider ECT as a first line antidepressant treatment in selected patients. Maintenance ECT should also be considered earlier rather than later in patients who relapse frequently despite adequate trials of maintenance medications.

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Response to Letter to the Editor from Andrade et al. (2003) ECT in the Management of Major Depression: Implications of Recent Research, *World J Biol Psychiatry* 4: 139-140.

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We are grateful to Dr. Andrade and his colleagues for their comments on the chapters in the WFSBP guidelines covering the use of electroconvulsive therapy (ECT) in unipolar depressive disorders and their additional recommendations for its safe use (Bauer et al 2002a, 2000b). Unfortunately, due to

limited space in these guidelines, we could not quote all case series and open studies that have been conducted on the use of ECT. With respect to the quotation of newer original data, only research articles published in peer-reviewed journals in English before August 2001 were considered. Therefore, many of the papers addressed by Andrade and colleagues were not available at the preset publication deadline. This was true for a recent excellent review that used sound methodology to summarise high quality evidence about the safety and efficacy of ECT for patients with depressive disorders (UK ECT Review Group 2003). The findings suggest that ECT is an effective short-term treatment for depression and is likely to be more effective than drug therapy (UK ECT Review Group 2003).

We certainly agree that ECT is an important treatment option, particularly for psychotic depression. However, there is an ongoing debate about the position of ECT in the armamentarium of biological treatments for depression. Many psychiatrists refuse to use it for ethical reasons. The intention of the WFSBP was to develop guidelines acceptable to the psychiatric community in different countries with different cultural and economic backgrounds (Möller et al 2002). Treatment-resistance and limits in the effectiveness of pharmacologic treatments have led to renewed interest in ECT. Although recent research has provided information about many issues related to the efficacy and safety of different ECT modalities, a number of questions remain for clinicians and patients. These include: Under which modalities and how frequently should ECT be administered in continuation and maintenance phase treatment? What are the long-term adverse effects of maintenance phase treatment? Is a combination of ECT and pharmacotherapy superior to ECT or pharmacotherapy alone? Is ECT a safe procedure for outpatients? If we can gain answers to these questions, ECT may become an increasingly important option for managing major depressive episodes and recurrent depressive disorders.

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Kuhlenbeck H (1954) The human diencephalon. A summary of development, structure, function and pathology. Karger, Basel.

Teuber HL (1964) The riddle of frontal lobe function in man. In: Warren T, Akert CH (eds) *The frontal and granular cortex and behavior*. McGraw-Hill, New York, pp 252-271.

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