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Implicit and explicit procedural learning in patients recently remitted from severe major depression

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ABSTRACT

In acute depression a high prevalence of deficits in learning and memory performance has been reported. Still, it is unclear whether these cognitive deficits are present after remission of clinical symptoms of depression. The present study compared 20 inpatients recently remitted from severe major depressive disorder (MDD) with 20 healthy matched control participants on two sequence learning tasks: a modified serial reaction-time task (SRT) for implicit learning, which is sensitive to subcortical and frontal impairments, and a serial generation task (SGT) for explicit learning. As compared with performance in healthy controls, implicit and explicit learning were not impaired in recently remitted inpatients with depression. Intentional acquisition of new information was related to the severity of depressive symptoms as patients with higher scores on Beck's Depression Inventory (BDI) showed poorer explicit learning. In contrast to findings in acute depression, our results suggest a normal degree of learning in remitted depression; these findings are consistent with unimpaired fronto-striatal functioning. However, although not statistically significant, patients remitted from melancholic MDD revealed poorer implicit learning performance compared with patients remitted from non–melancholic MDD. Longitudinal studies in patients with melancholic vs. non-melancholic MDD are needed to investigate the course of cognitive functioning during the recovery from MDD.

1. Introduction

Encoding and recognition of information have consistently been reported to be impaired in acute depression (meta-analysis by Zakzanis et al., 1998) and in bipolar depression (e.g. Bearden et al., 2006), but the evidence of cognitive dysfunctions in remitted depression is less clear-cut. An increasing number of studies have reported an unsatisfactory degree of remission in unipolar depression, and moreover, residual symptoms upon remission have been shown to have a strong prognostic value (cf. Fava et al., 2007). Only a few studies have examined cognitive functioning in patients recently remitted from major depressive disorder (MDD); however, a recent prospective study reported low episodic verbal memory performance to be a premorbid marker of depression (Airaksinen et al., 2007).

In this context awareness at retrieval seems to be a critical factor determining the degree of impairment, as depression has been demonstrated to impair effortful processing while interfering only minimally with automatic processing (review by Hartlage et al., 1993). Reber (1967) coined the term 'implicit learning' to describe participants' profiting from a probabilistic association between stimuli. This could be measured as a more efficient (faster) responding, i.e. performance increase is concomitant with practice even in the absence of awareness of the learned routine or skill.

To assess implicit memory performance independent of the current state of mood [mood-congruent memory effects as described by Bower (1981) are not reviewed here], neutral verbal stimuli were presented in most studies. Some of these studies reported impaired implicit learning of depressed participants (e.g. Elliot and Greene, 1992; Bradley et al., 1995; Tarsia et al., 2003), while a nearly equal number of studies revealed no significant differences between control subjects and depressed participants (e.g. Danion et al., 1991, 1995; Watkins et al., 1992, 1996; Ellwart et al., 2003) or individuals with anhedonia (Mathews and Barch, 2006). On the one hand, severity of depressive symptoms might contribute to these inhomogeneous findings, as it is related to cognitive performance (e.g. review by Hartlage et al., 1993). On the other hand, divergent results might reflect different experimental paradigms tapping different aspects of implicit learning, as implicit learning has been demonstrated to be impaired in a conceptual task, but spared in a data-driven perceptual task (Jenkins and McDowall, 2001).

The serial reaction-time task (SRT) introduced by Nissen and Bullemer (1987) allows an assessment of implicit learning without the

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confounding factor of language skills. Typically, mean reaction-time (RT) in the SRT decreases markedly when random stimulus presentation is replaced by a "hidden" cyclically repeated sequence of stimuli. As the RT savings occur even though participants are not aware of the repeating sequence, improved RTs during sequential trials reflect the degree of implicit sequence learning. Naismith et al. (2006) reported reduced implicit sequence learning in acute depression when implementing a standard SRT paradigm. The lower rates of implicit learning in depressive patients were associated with poorer mental flexibility, slower visuo-motoric speed as well as longer duration of the depressive episode. However, in a modified non-spatial SRT version, no performance deficits in implicit learning were obtained in depressed patients (O'Connor et al., 2005).

The only imaging study implementing a SRT paradigm in (geriatric) depressive patients revealed significantly decreased prefrontal activation and increased striatal activation during explicit sequence learning, but no significant differences in activation during implicit learning compared with controls (Aizenstein et al., 2005). Regarding the behavioral data, the depressive patients were impaired in implicit sequence learning (accuracy), but revealed spared explicit learning. Imaging studies in healthy subjects have consistently shown the basal ganglia, in particular the striatum, in interaction with cortical and cerebellar structures, to be implicated in the non-conscious acquisition of sequences (Rauch et al., 1995, 1997, 1998; Berns et al., 1997; Peigneux et al., 2000; Schendan et al., 2003; Thomas et al., 2004). Moreover, the primary motor cortex, the premotor cortex, and the supplementary motor area seem to be important motor-associated components of this cortico-striatal circuit subserving implicit learning in the SRT (Grafton et al., 1995, 2002; Hazeltine et al., 1997; Exner et al., 2006). The critical role of the cortico-striatal circuitry for SRT performance has also been established in patients with striatal pathology, such as Parkinson's disease (e.g. Pascual-Leone et al., 1993; Doyon et al., 1998).

To our knowledge, this study was the first to investigate implicit *and* explicit sequence learning in a group of remitted MDD patients. We implemented procedurally equivalent paradigms, a prerequisite to examine a dissociation of implicit and explicit performance. Still, the two conditions might differ with respect to their psychometric properties (cf. Chapman and Chapman, 2001). Additionally, we focussed on the possible contamination of implicit performance by the use of intentional retrieval strategies (Richardson-Klavehn and Bjork, 1988), as participants cannot be prevented from utilizing explicit memory strategies.

The aim of the present study was (1) to examine implicit *and* explicit sequence learning in recently remitted major depressive patients compared with healthy control subjects, and (2) to investigate whether implicit and explicit learning performance were related to neurocognitive functioning, severity of symptoms or melancholic subtype.

2. Methods

2.1. Subjects

Twenty inpatients diagnosed by the Structured Clinical Interview for DSM-IV (SCID-I) fulfilled the DSM-IV criteria for current MDD (subtype: melancholic ($N=10$) vs. non-melancholic ($N=10$)). They were tested as inpatients after remission defined as HDRS score ≤ 8 (Hamilton Depression Rating Scale; Hamilton, 1960). The SCID-I and the HDRS were completed by two trained clinical psychologists. Three patients had a comorbid anxiety disorder; all other axis-I psychiatric disorders were used as exclusion criteria. Patients with any history of neurological disorders, serious head injury, tardive dyskinesia, illegal drug use or alcohol abuse, and suicidal patients were excluded from the study. All patients received antidepressant treatment; 12 patients were medicated with low dosages of an atypical neuroleptic (chlorpromazine-equivalent daily dosage 210.0 ± 304.0 mg (mean $\pm$ S.D.); chlorpromazine-equivalent dosage converted according to Bezchlibnyk-Butler and Jeffries, 2001; Woods, 2003), and three patients received mood stabilizers. None of the patients received benzodiazepines at the time of testing. Twenty healthy controls matched for age, sex, and education were recruited from the hospital staff and from the community. Control subjects had no history of mental disorders (diagnosed by SCID-I) or any first-degree relatives with a history of mental disorders. All participants were native speakers of German with unimpaired visual performance. The study protocol was approved by the local ethics committee according to the Declaration of Helsinki of 1964, and written informed consent was obtained from all participants prior to their enrolment in the study. The groups did not differ from each other in any of the socio-demographic characteristics (see Table 1).

2.2. Clinical and neuropsychological assessment

Severity of depressive symptoms was rated by an experienced and trained clinician with the HDRS. The BDI (Beck Depression Inventory, Beck et al., 1961) was used to assess self-reported depressive symptoms during the last week. At admission to the psychiatric department, patients suffered from severe symptoms of depression documented by a mean HDRS score of 20.5 ± 8.9 and a mean BDI score of 23.3 ± 10.3. During treatment patients remitted from MDD (HDRS ≤ 8), and at the time of testing mean HDRS scores and mean BDI scores had improved significantly (HDRS: 3.9 ± 2.8, $t(19) = -7.63$, $P = 0.001$; BDI: 10.9 ± 6.5, $t(19) = -4.16$, $P = 0.002$). Intellectual performance was assessed by the Multiple Choice Vocabulary Intelligence Test (MWT-B; Lehrl, 1991), which is substantially correlated with full scale IQ on the Wechsler Adult Intelligence Scale-Revised (Satzger et al., 2002). Global verbal memory performance was measured by the Auditory Verbal Learning Test (AVLT; Helmstaedter et al., 2001). A common German Timed Test of Selective Attention (d2; Brickenkamp, 1981) was used to measure attentional performance. This test was designed to differentiate between the speed and accuracy of attentional performance by asking participants to mark target items presented in 14 long rows as quickly and accurately as possible, while skipping distracting non-target items. The groups did not differ from each other in any of the neuropsychological measures (Table 1).

2.3. Serial reaction-time task (SRT)

We used a modification of the SRT designed by Nissen and Bullemer (1987): The single stimulus appearing on each trial was a bright yellow

Table 1
Demographic variables, clinical characteristics, and cognitive measures.

Variable	Remitted MDD patients ($N=20$)	Control subjects ($N=20$)	Statistics	P
Age (years)	36.2 ± 9.6	35.1 ± 8.9	$t(38) = -0.38$	0.709[a]
Sex (male:female)	10:10	10:10	$\chi^2(1) = 0.00$	1.00[a]
Education (years)	11.9 ± 1.6	11.9 ± 1.6	$t(38) = 0.10$	0.922[a]
Age of onset of depression (years)	27.7 ± 11.5	–		
Cumulated life-time depression (month)	30.5 ± 55.6	–		
Intellectual performance (MWT-B predicted IQ-score)	116.8 ± 14.9	120.9 ± 14.4	$t(38) = 0.87$	0.390
Verbal memory				
AVLT[b] sum score (trial 1–5)	55.3 ± 7.7	54.2 ± 7.6	$t(38) = -0.46$	0.652
AVLT[b] recall (correctly recalled after 30 min)	12.0 ± 2.5	11.0 ± 2.5	$t(38) = -1.18$	0.248
AVLT[b] recognition (corrected for errors)	13.4 ± 1.8	12.5 ± 2.5	$t(38) = -1.36$	0.182
Attentional performance				
d2[c] speed (corrected for errors)	429.3 ± 70.9	439.0 ± 86.1	$t(38) = 0.38$	0.704
d2[c] accuracy (errors in %)	4.6 ± 3.1	2.8 ± 3.1	$t(38) = -1.68$	0.100

[a] Controls were matched according to age, sex and education.
[b] Auditory Verbal Learning Test (Helmstaedter et al., 2001).
[c] Timed Test of Selective Attention (Brickenkamp, 1981).