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Research report

Neurocognitive dysfunction in antidepressant-free, non-elderly patients with unipolar depression: Alerting and covert orienting of visuospatial attention

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Abstract

Background: Cognition is impaired across various domains in young and middle-age adults with unipolar depression. Performance appears in general worse in effortful tasks requiring executive function and attention. Probing specific cognitive operations in depressed patients, such as alerting and covert orienting of visuospatial attention, can better define and characterize the pathophysiology.
Methods: Nine antidepressant-free, clinically depressed patients and fourteen age-matched healthy subjects performed a Posner task with components of phasic alerting and covert orienting of visuospatial attention. Reaction times were analyzed by repeated-measures ANOVA with DIAGNOSIS as the between-group measure. Visual field (FIELD), stimulus onset asynchrony (SOA), and orienting CUE condition were within-subject, repeated measures.
Results: ANOVA showed intact attentional orienting in both groups. There were no FIELD differences across groups nor main effects of DIAGNOSIS. Interactions of DIAGNOSIS with SOA and DIAGNOSIS with CUE condition identified a phasic alerting deficit in the depressed patients. There were no significant effects of time-on-task, suggesting adequate vigilance or sustained attention in both groups. Plotting depressed versus control subjects' reaction time for each task condition (Brinley plot) showed linearity with a slope of 1.6 (i.e., patients were 1.6-fold slower) and a correlation coefficient of 0.98 (accounting for 96% of the overall variance).
Limitations: This study contains a small sample with potential for Type II error. The study addressed depression at the syndrome level. Depressed patients selected on particular symptom dimensions (e.g., anxiety, psychomotor retardation, etc.) could reveal abnormalities in hemisphere asymmetries that were not observed here.
Conclusions: These data highlight that global slowing is a major cognitive deficit in depression and arises across levels of difficulty. Putative specific deficits in depression need adjustment for the large effects of global slowing which can mimic selective impairments in more effortful task conditions.

Keywords: Arousal; Attention; Alerting; Orienting; Depression; Global slowing; Locus coeruleus; Noradrenergic; Schizophrenia; Chronometry

Clinical neuroscience needs to address fundamental issues when facing the syndrome of unipolar major depression. How do the interactions between affect and cognition go awry in mood disorders? What are the

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cognitive consequences for the depressed patient? Which physiological mechanisms become disturbed?

Traditional neuropsychological tests have revealed multiple domains of cognitive dysfunction in unipolar depression. Deficits have been reported in spatial learning, memory, and digit span (Gruzelier et al., 1988); explicit, declarative memory (Danion et al., 1991); selective attention and set-shifting (Austin et al., 1999), but see (Elliott et al., 1996; Purcell et al., 1997); free-recall (Ilsley et al., 1995); frontostriatal processing (reviewed in Rogers et al., 1998); attention, executive function, and visuospatial learning and memory (Porter, 2003); and frontal executive functions (Beats et al., 1996; Fossati et al., 1999; Fossati et al., 2003; Goodwin, 1997). A meta-analysis of neurocognitive dysfunction in major depression found that the largest effect sizes across studies arose in tests of encoding and retrieval of episodic memory (Zakzanis et al., 1998). Depressed patients have greater difficulty with effortful, attention-demanding tasks that require sustained attention (Cohen et al., 1982; Roy-Byrne et al., 1986; Spring, 1980).

In contrast, a relatively large group ($N=123$ patients) of young, unmedicated outpatients with mild to moderate unipolar depression had largely intact cognitive functions (Grant, 2001). Thus, the specific deficits found across studies appear sometimes inconsistent and contradictory. The most frequent explanation for the differing results relates to between-subject differences (age, presence of psychosis; medications; psychomotor retardation; length and severity of illness; comorbidities; etc.).

Disturbances in attention could account for the panoply of observed neurocognitive dysfunction. The attention system consists of a distributed array of neural networks that have several inter-related functions in control of cognition (Posner and Petersen, 1990). Selective attention serves to focus processing for allocating mental resources to a particular object or location. One mechanism for selecting a location is an eye movement, but another is the covert (i.e., without eye movements) orienting of attention to visual space. Such covert orienting occurs quickly, on the order of 50–100 ms. Another function of the attention system (sustained attention or vigilance) maintains task readiness. Over intervals of minutes to hours of time-on-task, performance disintegrates without special effort (e.g., the radar operator's night vigil). In contrast, attention has mechanisms for speeded processing limited to single trials, a process called alerting or phasic alerting. Orienting and alerting have separate physiological mechanisms and neurochemical modulators (Davidson and Marrocco, 2000; Fernandez-Duque and Posner, 1997; Witte et al., 1996; Witte and Marrocco, 1997). Humans also have differing levels of arousal that change throughout the day over a period of hours. The tonic level of arousal varies: alertness, drowsiness, sleep, obtundation, and coma. The detailed mechanisms involved in the tonic regulation of arousal and phasic alerting remain uncertain.

The extant literature relevant to attentional functions in depression was reviewed by Mialet et al. (1996). That review questioned the specificity of attentional deficits in depression: cognitive dysfunction might result from "a final common pathway" seen in many different mental disorders (e.g., schizophrenia: Chapman and Chapman, 1978).

At the level of the cerebral hemispheres, the non-dominant (generally right) hemisphere participates in sustained attention (Liotti et al., 1991; Pardo et al., 1991; Whitehead, 1991) and plays a major role in emotional regulation (Flor-Henry, 1979; Tucker, 1981). Consistent with this view, differential right hemispheric dysfunction has been observed in patients with unipolar depression (e.g., Banich et al., 1992; Goldstein et al., 1977; Kronfol et al., 1978; Lawrie et al., 2000; Miller et al., 1995). In contrast, patients with schizophrenia show state-dependent hemispheric asymmetries consistent with dysfunction in the left hemisphere (Maruff et al., 1995; Posner et al., 1988).

Unipolar depression may affect specific brain regions, individual cerebral hemispheres, or the whole-brain. One possibility is dysfunction in regions serving specific cognitive operations (e.g., memory encoding, lexical processing, etc.), while sparing others. Such pathophysiology suggests a hit-or-miss mechanism and could account for differing and inconsistent results in different groups of depressed patients. Another possibility concerns insult at the whole hemisphere level. Deficits at the hemisphere level should follow classical neuropsychological tests that differentially tap one hemisphere more than the other; the extant literature does not conclusively show such effects in unipolar depression. Alternatively, subcortical or specific damage to right brain regions supporting vigilance would affect more global process such as sustained attention, phasic alertness, or arousal. These matrix functions of attention involve broad neuromodulatory mechanisms.

Studies of speeded cognition have found a common process in aging and disease populations: global slowing. For example, elderly subjects show differential impairments on more difficult tasks as compared to young controls, but the differential is strictly proportional to the reaction time of controls (reviewed in White et al., 1997). In other words, there is a differential effect