

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.

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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

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

in reaction time between groups, where more difficult and effortful tasks take proportionately longer in one group over the other. Global slowing would predict that the depressed subjects perform in a consistently (and proportionately) slow manner when compared to the controls, regardless of the difficulty or type of task. The pathophysiology that underlies global slowing is not yet known.

To further study neurocognitive dysfunction in unipolar depression, we selected a task probing several cognitive operations within the attention system, rather than a classical neuropsychological test that examines multiple complex behavioral processes. The use of a simple task enables better dissection of the deficits in information processing at the level of elementary cognitive operations. The Posner paradigm for covert orienting of visuospatial attention (COVAT), with and without cues (Posner et al., 1984), has the potential to dissect levels of attentional impairment associated with depression. If depression disrupts the processing of the whole right hemisphere, several abnormalities should be seen. Dysfunction in right parietal regions should demonstrate asymmetries in the orienting of attention. Dysfunction in right prefrontal regions may demonstrate diminished vigilance functions with slowing becoming greater as time-on-task increases. Indeed, this paradigm has identified subtle left hemisphere abnormalities in schizophrenia (Maruff et al., 1995; Posner et al., 1988), so has inherent sensitivity to detect right hemisphere abnormalities in this application. If depression assaults individual cognitive operations (cueing, moving, engaging, and disengaging of visuospatial attention), specific conditions of the task should reveal selective impairments even after correcting for global slowing. If depression disrupts the matrix functions of attention throughout the cortex, global slowing effects should appear. We were mainly interested in studying unipolar depression as a syndrome without regard to state effects such as level of sadness, anxiety, melancholia, psychomotor retardation, etc.

To the best of our knowledge, there is one previous application of the Posner paradigm focused on unipolar depressed patients (Smith et al., 1995). That study specifically sought to examine the relationships between psychomotor retardation, motor planning, and mental slowing. The paradigm used by Smith et al. is very different than used here: two response keys; very short SOAs (0–200 ms); absence of a no cue condition (NO); and inclusion of patients taking antidepressants. As the questions addressed and the experimental paradigms were different, a direct

comparison between the two studies is difficult. Nevertheless, the depressed patients in the Smith et al. study showed a main effect of diagnosis on reaction times (patients' reaction times were slowed) as well as a normal validity effect, i.e., reaction time difference between valid versus invalidly cueing. Also, one block containing only 96 trials minimized the load on sustained attention or vigilance. Here, we study young and middle-aged patients with moderately severe unipolar depression before treatment with antidepressants and an age-matched control group in the Posner paradigm with three blocks and longer SOA to assess the relative contributions of specific cognitive deficits, sustained attention, and generalized arousal dysfunction.

1. Method

Patients were recruited after providing written informed consent according to institutional procedures. All depressed patients satisfied Feighner research criteria for primary affective disorder (Feighner et al., 1972) as well as DSM-IV criteria for major depression. Both inpatients and outpatients were recruited. Exclusion criteria included any concurrent major psychiatric disorder, e.g., alcoholism, drug abuse, etc. Chart reviews, when available, and unstructured clinical interviews (J.V.P.) provided diagnostic information. Table 1 displays the clinical characteristics of the nine patients (five female, four male; mean age 32 years, range 15–54 years). All patients were right-handed and were free of antidepressant medications for at least 1 month. The reasons why these patients were unmedicated did not relate to this study. Rather, patients had discontinued medications themselves; preferred psychotherapy over pharmacotherapy; or decided on a medication washout between trials. None were psychotic. The average Beck Depression Inventory score was 23 (range 18–35; S.D. 7.5).

Age-matched control subjects, who screened negative for psychiatric disorder with a highly sensitive computer-administered diagnostic questionnaire (Bucholz et al., 1991; childhood conduct disorder or simple phobias were not exclusionary), consisted of 12 females and 2 males. The average age was 31 years (range 18–60 years); 13 were right-handed and one was left-handed.

The present version of the paradigm for measuring covert orienting of visuospatial attention has been described in detail (Posner et al., 1984; see Fig. 1). Briefly, subjects sat in front of a video monitor. They maintained fixation on a mark in the center of the

Table 1
Clinical characteristics of patients with unipolar depression

Patient	Gender	Age	Education	Beck	Family history	Symptoms ^a	Current episode duration	Medication
1	F	45	12	20	N	1, 2, 3, 4, 5, 6, 7, 8	>1 week	Nadalol
2	F	15	9	19	N	2, 4, 5, 6, 7, 8	1 year	None
3	F	22	14	25	Y	1, 2, 3, 4, 5, 6, 8	Several months	None
4	M	21	13	18	N	2, 3, 4, 5, 6, 7, 8	5 months	None
5	M	50	13	24	Y	1, 3, 4, 5, 6, 7, 8	4 months	Chlorazepate
6	F	20	15	35	Y	1, 2, 3, 4, 5, 6, 7, 8	4 months	None
7	M	33	16	18	Y	2, 3, 4, 5, 7	Several months	None
8	F	32	16	30	Y	2, 3, 4, 5, 6, 7, 8	1 month	None
9	M	54	13	24	Y	3, 4, 5, 6, 7, 8	Several months	None

^aSymptoms: 1, change in appetite or weight; 2, sleep disturbance; 3, psychomotor changes; 4, anhedonia or loss of libido; 5, decreased energy; 6, feelings of hopelessness, worthlessness, or guilt; 7, diminished concentration; 8, thoughts of death or suicide.

monitor screen and pressed as quickly as possible a reaction time key using the index finger of the dominant hand whenever the target, an asterisk, appeared in the center of either the left or right visual field target regions. Intermittent visual inspection for eye movements ensured compliance with fixation instructions. The target regions were dim squares (1°) about 5° to the left or to the right of the fixation mark. Trials, presented 1 s after the last key press, were arranged in three blocks (“BLOCK”, 240 trials) with five rest breaks within each block. Pressing the response key immediately erased the screen until the next trial. Both the target regions and the fixation mark would then reappear. On some trials, one target region became brighter at 1 s following the start of the trial, indicating a high probability (80%) that the target would appear there. The target would appear either 100 or 800 ms after the cue onset (i.e., stimulus onset asynchrony—SOA). Cues and targets were balanced and randomized with respect to side of presentation. Subjects would thus either get no cue as to the laterality of the target (“NO”—20% frequency per block), a correct cue as to the location of the target (“VALID”—64% frequency per block), or an incorrect cue (“INVALID”—16% frequency per block). Of note, NULL cue has been used to designate either the NO cue condition used here, or the condition where an alerting cue occurs without spatial information (e.g., screen, fixation mark, or bilateral target regions brighten, e.g., Townsend et al., 1999), not used here.

2. Results

The median reaction time for detecting the target for each block under each condition (NO, VALID, INVALID) was calculated after eliminating all response times less than 100 ms (probable anticipations) or greater than 3 s (maximal trial duration—probable omissions). These errors were not significantly different between depressed and control groups (9% vs. 5%, respectively; $F(1,21)=1.46$, $p<0.24$). The reaction time data were analyzed using ANOVA with DIAGNOSIS (i.e., depressed, control) as the between group variable. BLOCK (i.e., 1,2,3), CUE (i.e., NO, VALID, INVALID), SOA (i.e., 100, 800 ms), and visual FIELD of target (i.e., left, right) served as the within-group, repeated measures variables.

As expected, the main effects involved CUE, $F(2,42)=107$, $p<0.0001$; SOA, $F(1,21)=72$, $p<0.0001$; and FIELD, $F(1,21)=7.7$, $p<0.01$ as well as an interaction of CUE with SOA, $F(2,42)=10.8$, $p<0.0002$ (Posner et al., 1984; Posner et al., 1988; Whitehead, 1991; Swanson et al., 1991). There were no detectable main effects of DIAGNOSIS, $F(1,21)=2$, $p<0.17$ nor interactions involving FIELD (e.g., DIAGNOSIS by FIELD; DIAGNOSIS by FIELD by CUE; etc.). In particular, there was no evidence for an abnormality in the covert orienting of attention in depressed patients (i.e., DIAGNOSIS by CUE by SOA by FIELD, $F(2,42)=0.3$, $p<0.7$). Other noteworthy interactions included DIAGNOSIS by CUE, $F(2,42)=8.5$, $p<0.0008$, and DIAGNOSIS by SOA, $F(1,21)=3.7$,

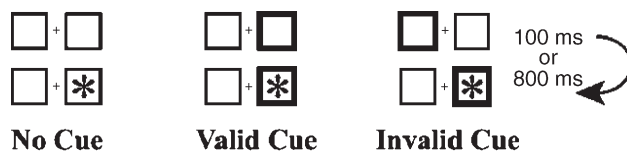


Fig. 1. Paradigm for alerting and covert orienting of visuospatial attention (Posner's COVAT).

Table 2

Mean of median reaction times (milliseconds) from three blocks of trials as a function of DIAGNOSIS (depressed, control); visual FIELD of target (LEFT, RIGHT); CUE condition (NO, VALID, INVALID); and stimulus onset asynchrony (SOA, 100 ms, 800 ms)

	Left						Right					
	No		Valid		Invalid		No		Valid		Invalid	
	100	800	100	800	100	800	100	800	100	800	100	800
<i>Depressed</i>												
Mean	426	388	378	303	437	359	404	379	376	298	430	353
S.D.	77	33	39	57	67	48	51	38	54	60	65	54
<i>Control</i>												
Mean	368	340	347	305	376	335	356	338	335	289	383	327
S.D.	61	62	62	86	56	78	63	64	70	74	70	78

$p < 0.067$. No main effects or higher order interactions involving BLOCK reached significance. Therefore, the reaction time means and standard deviation of the medians for all three blocks as a function of CUE, SOA, and FIELD are shown in Table 2; the means are displayed graphically in Fig. 2.

Analysis of variance of contrast variables for significant effects revealed noteworthy post hoc comparisons. The depressed patients, like normal controls, understood and used the cue information since the reaction time in the valid cue condition was faster than the reaction time in the invalid cue condition, $F(1,21) = 112$, $p < 0.0001$. The performance of depressed and control subjects in the valid condition, containing both alerting and the correct spatial information, was similar at both SOA's. However, depressed patients had greater costs from invalid cueing at both SOAs. The validity

effect (i.e., reaction time difference between invalid and valid cue conditions) was greater in the depressed group than in control subjects, $F(1,21) = 12.9$, $p < 0.002$. Compared to the NO cue condition, both depressed patients and controls showed a decrease in reaction time when a target is presented at the cued location (i.e., valid cue condition), $F(1,21) = 37.7$, $p < 0.0001$. Such facilitation can be attributed to the phasic alerting effects of the cue as well as the cue's information content. Note that depressed patients had greater improvement than normal controls, $F(1,21) = 13.0$, $p < 0.002$ (i.e., NO compared to VALID). This appeared to arise from the greater cost of invalid cueing in the depressed patients, especially at short SOA. Compared to the NO cue condition, however, the depressed patients were not statistically different than normal controls when the invalid target appeared contralateral to the cued

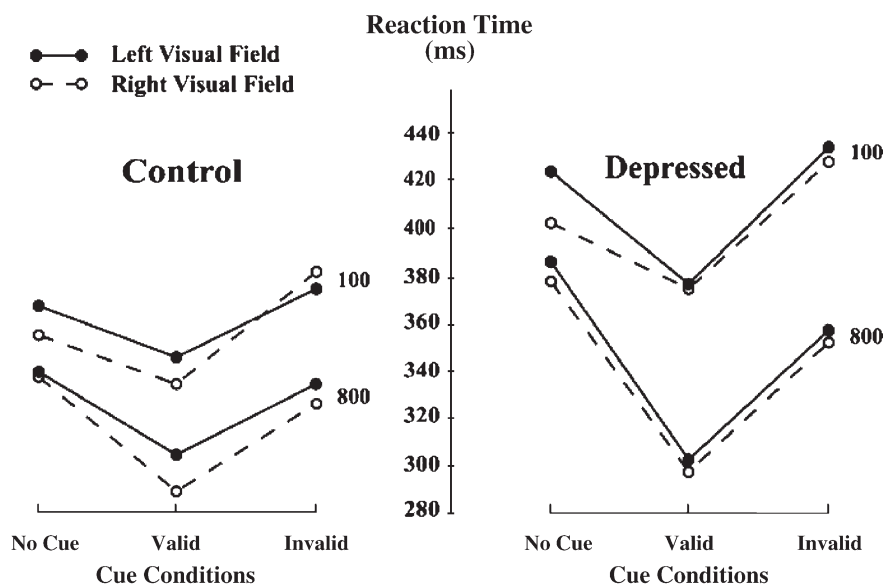


Fig. 2. Data from Table 2 presented graphically.

location (NO vs. INVALID), $F(1,21)=0.46$, $p<0.5$. The interaction of DIAGNOSIS with SOA, which approached significance, $F(1,21)=3.7$, $p<0.067$, showed that depressed patients get greater gains than controls when the time between the cue and target is increased from 100 to 800 ms. The absence of a main effect of BLOCK, $F(2,42)=0.5$, and the absence of any significant interactions involving BLOCK argue against the potential confound of fatigue in the depressed patients.

The above noted interactions of DIAGNOSIS by CUE ($p<0.0008$) and DIAGNOSIS by SOA ($p<0.067$) parallel recent findings in the literature on cognitive aging. Older adults perform more slowly than young adults on a wide variety of tasks. Furthermore, the discrepancy in performance between old and young adults increases with task difficulty. Analysis of reaction time data using ANOVA shows ubiquitously an interaction of AGE (old vs. young) by TASK CONDITION. This interaction effect is believed to reflect a unitary mechanism called general cognitive slowing, a phenomenon associated with aging and presumed to reflect altered arousal (Cerella, 1994; Myerson et al., 1990). Therefore, the reaction time data displayed in Table 2 were reanalyzed using a Brinley plot (Brinley, 1965). The Brinley plot graphs the relationship of the reaction time data of the depressed patients as a function of the reaction time data of the normal controls for a wide variety of tasks. In the present application, each of the twelve conditions of the paradigm for covert orienting of attention (see columns in Table 2) relates to a particular TASK CONDITION. Fig. 3 demonstrates

that the latency data fit a linear function with slope 1.6 (correlation coefficient of $r=0.98$ accounting for 96% of the variance). Therefore, the depressed subjects perform 1.6 times slower than the normal controls for any given cueing condition (or 63% slower than controls).

3. Discussion

Global slowing surfaced as the major deficit in this study and accounted for 96% of the overall variance. Depressed subjects performed 1.6-fold slower than did the controls for any given task condition. No deficits in specific attentional operations were detected (e.g., move, engage, disengage). The result is consistent with reports showing in depressed patients greater difficulty and slower performance as the task complexity increases. These results converge with a meta-analysis that finds general global slowing (i.e., task-independent) accounting for the apparently specific deficits found in unipolar depression (White et al., 1997).

A phasic alerting deficit surfaced in depressed patients. An interaction between DIAGNOSIS and CUE, with greatly slowed reaction times in the no cue condition, is consistent with depressed patients being more sensitive to the absence of alerting in the no cue condition (i.e., hypoarousal). Also, the difference between NO and VALID reaction times was greater in the depressed group compared to the control group, particularly at the long SOA, when the effects of phasic alerting should appear. The DIAGNOSIS by SOA interaction suggests that overall, across cue conditions, depressed patients show greater improvements in

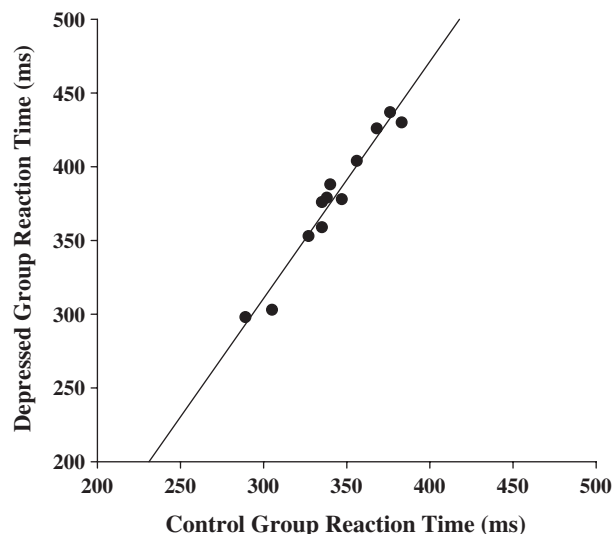


Fig. 3. Brinley plot of mean reaction time of patients with unipolar depression vs. mean reaction time of healthy controls for each condition of the Posner paradigm (COVAT).

reaction time at 800 ms SOA than at 100 ms. The faster reaction times at the 800 ms SOA than at 100 ms are consistent with the known time course of visuospatial attention effects (early, 50–100 ms) and phasic alerting effects (late, 400 ms and greater), respectively. The validity effect (i.e., difference in reaction time between VALID and INVALID) was greater in patients than in controls. Depressed patients suffer greater costs in the INVALID condition. This may reflect an affective bias for greater costs following incorrect orienting.

This investigation had several strengths: 1) young and middle aged subjects; 2) both inpatients and outpatients with serious, clinical depression free of confounding diagnoses; 3) simple task paradigm readily performed by even very ill or brain-damaged patients; 4) absence of antidepressant medications, which could potentially alter pathophysiology; and 5) quantitative analysis of global slowing demonstrating its severity in the depressed group.

A secondary finding was the relative absence of hemispheric asymmetries in the covert orienting of visuospatial attention between groups. There was a main effect of visual field, but no interactions between FIELD and DIAGNOSIS. This result may run counter to previous reports of a selective deficit in right hemisphere processing in induced negative mood in control subjects and in unipolar depression (see Introduction), but converges potentially with a study of covert visuospatial orienting in two groups of psychotic patients with schizophrenia or affective disorders (Maruff et al., 1995). The absence of asymmetry in depression contrasts with findings from several chronometric investigations of acutely ill, schizophrenia patients who show significant left hemisphere deficits in covert orienting.

Here, the null finding concerning laterality must be qualified based upon several limitations of the current study: 1) small sample size and subsequent potential for Type II errors (although a similar number of schizophrenia patients can show significant asymmetry (Pardo et al., 2000)); 2) depressed patients and controls were not matched for gender (no gender effects upon asymmetry surfaced in the schizophrenic patients and controls, but gender effects have been reported in induced depressed mood); 3) absence of a long SOA (SOA greater than 3 s appears most sensitive for detecting hemispheric asymmetries in sustained attention in normal controls; and 4) asymmetries may depend on specific symptoms (e.g., anxiety, sadness, insomnia, etc.) rather than on the disease syndrome (this study addressed deficits associated with the syndrome and did not parcellate according to symptoms).

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