PERGAMON

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Journal of Psychiatric Research 38 (2004) 27–35

JOURNAL OF PSYCHIATRIC RESEARCH

www.elsevier.com/locate/jpsychires

Neuropsychological correlates of psychotic features in major depressive disorders: a review and meta-analysis

Shelley K. Fleming[a,b,*], Christine Blasey[a], Alan F. Schatzberg[a]

[a]*Department of Psychiatry and Behavioral Science, Stanford University School of Medicine, Stanford, CA 94305, USA*
[b]*Veterans Affairs, Palo Alto Health Care System, Palo Alto, CA 94304, USA*

Received 12 September 2002; received in revised form 29 May 2003; accepted 15 June 2003

Abstract

Neuropsychological functioning has been a focus of study in psychotic disorders for many decades. These studies have focused primarily on schizophrenia, and less so on the affective psychoses, including psychotic major depression PMD. Several studies have provided evidence of cognitive dysfunction in PMD. However, these studies have utilized different assessment methods and instruments. Consequently, a clear picture of the nature and severity of cognitive impairment in PMD has yet to emerge in the literature. The current review seeks to provide a summary of the literature by composing a quantitative and qualitative review of the research to date on the cognitive impairment in psychotic major depression, specifically as it contrasts to those deficits observed in nonpsychotic depression. This review also provides a summary model of the pathophysiology of PMD to provide the necessary context to understanding the biological mechanisms of these impairments.
Published by Elsevier Ltd.

Keywords: Neuropsychology; Cognitive; Psychotic; Depression; Cortisol

1. Introduction

Neuropsychological functioning has been a focus of study in psychotic disorders for many decades. The vast majority of these studies have focused on schizophrenia and have been primarily descriptive in nature. Investigators have described the neurocognitive "profile" of schizophrenia at different phases of the illness, including pre-onset vulnerability markers, deficits associated with acute psychosis, and residual deficits that remain as the acute symptoms abate (Spaulding et al., 1996). Researchers have correlated neuropsychological deficits with functional impairment in social and occupational skills, highlighting the real-world consequences of cognitive deficits for patients. These deficits have also been correlated with structural and functional brain anomalies with the goal of delineating the pathophysiology of schizophrenia and other psychotic disorders.

Fewer studies have focused on the neuropsychological deficits observed in affective psychotic disorders, such as major depression with psychotic features and bipolar disorder with psychotic features. As much of the work that does exist focuses on non-psychotic major depression (NPMD) and psychotic major depression (PMD), the current review will concentrate on these specific affective disorders. The literature is qualitatively and quantitatively reviewed. Lessons from the schizophrenia literature are incorporated where applicable, especially regarding the future directions of this research.

2. Clinical features and diagnosis of psychotic major depression

Approximately 25% of consecutively admitted depressed patients exhibit psychotic symptoms (Coryell et al., 1984). These symptoms usually consist of non-bizarre nihilistic, somatic, or guilty delusional beliefs and less often hallucinations or formal thought disorder. Considerable evidence supports PMD as a distinct subtype of depression, including stability of psychotic symptoms across depressive episodes

* Corresponding author at current address: VAPAHCS, 116B Psychology, 3801 Miranda Avenue, Palo Alto, CA 94304, USA. Tel.: +1-650-493-5000x63025.
E-mail address: shelleyf@stanford.edu (S.K. Fleming).

0022-3956/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/S0022-3956(03)00100-6

(Lykouras et al. 1985, Schatzberg and Rothschild, 1992), neurobiological findings (i.e., increased ventricle-to-brain ratio) (Rothschild et al., 1989; Simpson et al., 1999), and treatment response (i.e., antidepressant monotherapy is often insufficient; presence of psychotic features is predictive of better response to ECT) (Schatzberg and Rothschild, 1992). Of these, differential treatment response speaks directly to the need for accurate diagnosis. Additionally, presence of psychotic features is predictive of increased risk of suicide (Roose et al., 1983). However, accurate diagnosis is often hampered by the plausibility of the patient's report and by relatively preserved insight, which may result in unwillingness to disclose critical diagnostic information related to the psychotic symptoms. For this reason, Schatzberg and Rothschild (1992) proposed that clinicians rely on alternate sources of information, specifically neuropsychology, to inform diagnosis and treatment planning.

Neuropsychological assessment is an ideal strategy for obtaining corroborative data in a psychiatric population due to the presumed absence of self-report bias. The current review proposes a specific instance in which neuropsychological assessment may inform differential diagnosis of depressive disorders in general clinical settings. We begin by providing a model of the pathophysiology of psychotic symptoms in major depression. This model provides the foundation for interpreting the neuropsychological literature and serves an essential function in promoting the application of neuropsychological data in clinical practice.

3. Pathophysiology of psychotic symptoms in major depressive disorders

Hypothalamic–Pituitary–Adrenal (HPA) axis hyperactivity is a fundamental component of current pathophysiological models of the acute psychosis as the HPA axis has extensive interconnections with subcortical dopamine systems implicated in psychotic symptom expression. Support for interactions between dopamine systems and the HPA axis is largely based on animal research. These studies suggest that HPA axis activation and subsequent cortisol release stimulates dopamine metabolism in striatal cells, including the nucleus accumbens and mesolimbic system (McEwen et al., 1993). Additionally, both cortisol and dopamine increases have been observed in response to acute environmental stress (Antelman and Chiodos, 1984; Grossman, 1993) and biochemically induced stress (Breier et al, 1988; Wolkowitz et al., 1989). Furthermore, the relationship between HPA axis activation and dopamine metabolism appears to be dose-dependent with higher levels of cortisol associated with higher rates of dopamine metabolism. This effect has been observed in schizophenia and affective disorders, as well as normal control groups (Walker and DiForio, 1997).

Several neurotransmitter systems are regulated by this system, in terms of biosynthesis and modulation of receptor complexes (Antelman and Chiodo, 1984). For example, stress-related changes have been identified in gamma-aminobutyric acid (GABA), glutamate, serotonin, and dopamine systems. HPA axis activity has also been implicated in dopamine receptor sensitivity and density. Specifically, dopamine receptor subtypes in the nucleus accumbens are differentially affected by prenatal stress in rats. Additionally, Lindley, et al. (1999) reported decreased dopamine utilization in mesocortical and nigrostriatal regions in response to sustained administration of corticosterone in rats. Similarly, Lyons et al. (2000) reported that cortisol administration associated with decreased dopamine turnover in prefrontal cortex disrupts performance on a prefrontal cortex-mediated, barrier reach task in monkeys similar to effects seen in other studies when dopamine turnover by prefrontal cortex is affected by phencyclidine. Taken together these data suggest HPA axis-dopamine interactions in the prefrontal cortex may lead to deficits on tasks requiring attention and response inhibition. In the area of schizophrenia research, increasing attention has been paid in recent years to cognitive deficits and negative symptoms consistent with decreases in prefrontal dopamine activity or metabolism.

Neuropsychological impairments associated with HPA axis dysregulation have been identified in the domains of attention/concentration, psychomotor speed, and memory. These processes are largely mediated by the frontal and temporal regions. Executive level processes, such as abstraction and conceptual processing, may also be susceptible to HPA axis dysregulation given their reliance on frontal cortex integrity (Kolb and Wishaw, 1996). The relationship between neuroendocrine processes and neuropsychological functioning may be related to the degree of overlap between glucocorticoid receptor sites and anatomical substrates of task performance. With respect to the HPA axis, two types of adrenal steroid receptors have been identified in the CNS and periphery. Type I receptors primarily bind mineralocorticoids (MR; e.g., aldosterone) while Type II receptors bind glucocorticoids (GR). These receptors may be located within the same cells although they are produced by different genes (McEwen et al., 1993). Of the two receptor types, the high affinity MR type is found more abundantly in hippocampus than is the GR type. There is some debate as to the extent to which GR is present in primate hippocampus; however, the discrepant results may stem from methodological differences related to the probe utilized in the different studies. In contrast, several studies indicate high density of GR in rats in the medial regions of the frontal cortex

(Diorio et al., 1993) as well as in primates (Sanchez et al., 2000; Patel et al., 2000).

Regardless, research in normal controls and physical disorders, such as Cushing's disease, has identified specific cognitive impairments associated with HPA axis anomalies. These impairments are almost exclusively within the domains of attention and memory functioning. For example, Born et al. (1987) found that attentional processes are disrupted by exogenous cortisol administration in normal volunteers. Exogenous corticosteroid administration in normal volunteers also has been related to deficits in free recall performance (Wolkowitz et al., 1993), declarative memory (Newcomer et al., 1994) and verbal memory deficits (Wolkowitz et al., 1990). Selective memory impairment has been found in patients with Cushing's disease, which is characterized by chronically high cortisol levels (Mauri et al., 1993). Further, memory deficits associated with Cushing's disease have been shown to remit after surgical intervention resulting in lowered circulating corticosteriod levels (Varney et al., 1984).

4. Neuropsychological functioning in PMD

A clear profile of neuropsychological impairment in PMD, as compared to NPMD, has yet to emerge. One study (Basso and Bornstein, 1999) suggested a pattern of global and diffuse neuropsychological impairment across measures of attention, speed of processing, visual-spatial abilities, learning, memory, and language. However, other studies have reported findings of more specific impairment.

Kim et al. (1999) reported specific impairment in abstract reasoning and conceptual processing in PMD as compared to NPMD using the Wisconsin Card Sort Test (WCST) in a geriatric sample. No between-group differences were found on measures of language (Boston Naming Test: Korean version), memory (California Verbal Learning Test, Visual Reproduction), or mental status. Simpson et al., (1999) also reported deficits on the WCST in a younger sample of PMD vs. NPMD patients. However, their finding was less specific as they also reported deficits in attention (Digit Span) and speed of processing (Trail Making Test). Of note, no between-group differences were observed on measures of immediate or delayed verbal memory (Rey Auditory Verbal Learning Test) in this study.

As suggested above, memory deficits have not been consistently observed in PMD. Schatzberg et al. (2000) reported significant impairment on verbal and visual memory measures. However, other studies have found no evidence of memory deficits (Jeste et al., 1996; Kim et al., 1999; Simpson, et al., 1999). These discrepancies may be explained by differences in test selection (e.g., word lists vs. stories; differences in task difficulty) or subject selection (e.g., medicated vs. unmedicated; inpatient vs. outpatient). It is also possible that memory deficits are an artifact of deficits in other domains, including speed of processing, attention and/or executive functioning.

Less variability is observed across studies on measures of speed of mental processing. In fact, every study that included a processing speed measure reported between-group differences in this domain. The Trail Making Test and the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were the most commonly used measures (Jeste et al., 1996; Schatzberg et al., 2000; Simpson et al., 1999).

Deficits on various aspects of attentional functioning were also relatively consistent across studies. Impairment was observed on measures of immediate auditory attention (Digit Span: Jeste et al., 1996; Simpson et al., 1999) response inhibition (Stroop Color Word Test: Schatzberg et al., 2000) and sustained attention and vigilance (Digit Vigilance Test: Jeste et al., 1996; Continuous Performance Test: Nelson et al., 1998). Interestingly, both Jeste et al. (1996) and Nelson et al. (1998) compared NPMD to PMD and schizophrenia (SCZ) patients. Collectively, their data suggest that sustained attention/vigilance, as measured by a continuous performance task, is specific to psychotic disorders as the PMD and SCZ groups were significantly and equivalently impaired on this task. Further, the neuropsychological profile of PMD is strikingly similar to SCZ in contrast to the marked differences observed between PMD and NPMD (Jeste et al, 1996; See Fig. 1).

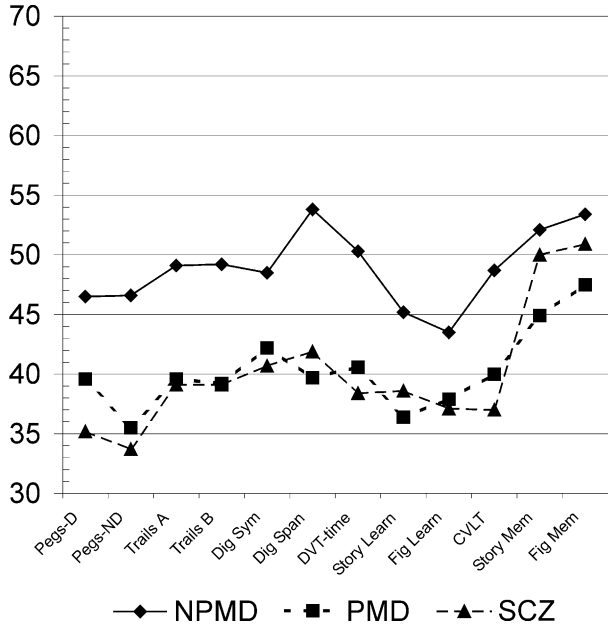

Fig. 1. Age and education-corrected *T*-scores of neuropsychological tests in non-psychotic major depression, psychotic major depression, and schizophrenia (Jeste et al., 1996).

Overall, neuropsychological deficits in PMD have been reported in attention and speed of processing. Deficits have also been reported in higher level executive processing, including abstract reasoning and conceptual processing; however, fewer studies have reported data within this domain. Memory impairment has been documented in some studies, but not in others. To more closely examine these discrepancies, we conducted a meta-analytic review of the current literature comparing PMD to NPMD on measures of neuropsychological functioning. The primary purpose of this analysis is to determine the magnitude of the between-group differences within and across specific cognitive domains. Because of the limited number of studies providing relevant data, variability of cognitive tasks utilized, variability of diagnostic criteria, and lack of statistical reporting to allow calculation of effect sizes this analysis is necessarily preliminary in nature.

5. Meta-analytic review of studies

5.1. Methodology

The literature search specific to neuropsychological functioning in Psychotic Major Depression included a review of citations listed in PsychInfo and Medline from 1980 to 2002 using the following key word searches: neuropsychology and depression, neuropsychology and psychotic depression, cognitive and depression, cognitive and psychotic depression. Depression was used as an inclusive term to capture as many relevant citations as possible; however, articles were only appropriate for the current purpose if the authors provided data on patients with Psychotic Major Depression as a subgroup. Additional references were acquired from the reference lists of the cited articles. Dissertations and dissertation abstracts were not included. In some cases, neuropsychological tests were reported that are not commercially available to the general public. For the most part, these manuscripts were not included in the review due to the difficulty in obtaining expert ratings on unfamiliar tests.

The comprehensive search of the published literature yielded seven articles that addressed cognitive deficits in Psychotic Major Depression. Of these studies, five were chosen by the consensus of two expert raters; their decisions based on whether a given study met all four of the following criteria: (1) the availability of sample means and standard deviations or other information that allowed for computation of an effect size (e.g., an F or t test statistic); (2) use of a non-psychotic comparison group; (3) use of standard and reliable diagnostic procedures to determine presence of psychosis; and (4) use of standardized, reliable, and valid neuropsychological tests. Lack of available data for effect size computation precluded two articles (Nelson et al., 1998; Rothschild et al., 1989). A description of these studies is included in the Discussion section.

Although predominantly qualitative in nature due to the limited number of studies available for review, meta-analysis was conducted on those five studies that addressed differences in neuropsychological functioning between patients with Psychotic Major Depression and Nonpsychotic Major Depression. Effect size (ES) was calculated when sufficient information (descriptive or inferential) was provided in the study. When means and standard deviations were reported, the ES was calculated by dividing the mean difference by the pooled standard deviation (Glass et al., 1981). When descriptive data were not reported, the ES were derived from inferential statistics using procedures set forth by Wolf (1986).

All studies relied on prospective data collection, with the exception of one study, which conducted a retrospective chart review of diagnostic notes (Basso and Bornstein, 1999). An overview of the five selected studies, including demographic and other information describing the psychotic major depression and control samples, is provided in Table 1.

5.2. Neuropsychological tests and constructs

Different neuropsychological measures were used across the six studies including: Stroop Color-Word test, Judgment of Line Orientation (JLO), Wisconsin Card Sort Test (WCST), Wechsler Adult Intelligence Scale-Revised (WAIS-R), Grooved Pegboard Test, Trail Making Test, Rey-Osterreith Complex Figure, Digit Vigilance Test, Controlled Oral Word Association Test, California

Table 1
Descriptive data for studies included in the meta-analytic review

Study	*N* NPMD	*N* PMD	Average age (S.D.): NPMD	Average age (S.D.): PMD	Medication Status	Phase of Illness	Hospitalization Status
Schatzberg et al. (2000)	32	11	43.10 (15.20)	40.60 (13.90)	Unmedicated	Acute	Outpatient
Jeste et al. (1996)	28	30	56.80 (10.30)	61.30 (12.00)	Mixed	Mixed	Outpatient
Basso and Bornstein (1999)	46	34	31.87 (7.30)	31.44 (7.28)	Mixed	Mixed	Inpatient
Kim et al. (1999)	26	19	65.12 (6.91)	64.84 (7.21)	Unmedicated	Acute	Inpatient
Simpson et al. (1999)	18	81	74.30 (5.80)	75.20 (4.60)	Medicated	Remitted	Inpatient

Verbal Learning Test, Wechsler Memory Test-Revised (WMS-R). Unless otherwise noted, references for these measures can be found in Spreen and Strauss (1998). A board-certified clinical neuropsychologist, blinded to the current study's goals and hypotheses, was asked to read the list of standardized tests and identify the neuropsychological construct that is assessed by each test (e.g., JLO is a measure of spatial orientation and perception). The neuropsychological tests and the corresponding constructs are presented in Table 2.

6. Results

Individual effect sizes were calculated for each standardized measure (See Table 3). Average standardized differences were then calculated by averaging the effect sizes within five cognitive domains: visual-spatial skills, psychomotor speed, attention, memory, and executive functioning (See Fig. 2). The domains were intentionally very broadly defined due to the limited number of studies available. However, as the literature base increases analysis of more specific processes (e.g., immediate memory vs. delayed memory vs. recognition) will be allowed.

Table 2
Neuropsychological measures within each cognitive domain for the meta-analytic review

Construct	Test
Attention	Digit Vigilance Test-errors
	Digit Vigilance Test-time
	Stroop Color Word-color/word score
	WAIS-R Digit Span
	WAIS-R Digit Span (forward)
	WAIS-R Digit Span (fbackward)
	WMS-R Visual Span (forward)
	WMS-R Visual Span (backward)
Executive function	Wisconsin Card Sorting Test-% perseverative errors
	Wisconsin Card Sorting Test-categories completed
	Wisconsin Card Sorting Test-perseverative errors
	Wisconsin Card Sorting Test-total errors
	Controlled Oral Word Association Test
Memory	California Verbal Learning Test-short delay free recall
	Paragraph Recall Test-Delayed Memory
	Rey Auditory Verbal Learning Test-delayed recall story recall
	WMS-R Logical Memory II
	California Verbal Learning Test-short delay cued recall
	California Verbal Learning Test-sum of trials 1-5
	Paragraph Recall Test-Immediate Memory
	Rey Auditory Verbal Learning Test-trial 5 story learning
	WMS-R Logical Memory I
	Rey-Osterrieth Complex Figure-memory
	WMS-R Visual Reproduction II figure learnng
	WMS-R Visual Reproduction I
Psychomotor speed	Grooved Pegboard Test-dominant hand
	Grooved Pegboard Test-nondominant hand
	Trail Making Test-A
	Trail Making Test-B
	WAIS-R Digit Symbol
Visual-spatial	Judgment of Line Orientation
	Rey-Osterrieth Complex Figure-copy
	WAIS-R Block Design

6.1. Visual spatial skills

Three studies (Schatzberg, Jeste, and Simpson) reported visual-spatial ability data, derived from the WAIS-R Block Design, Rey Complex Figure-copy, and the Judgment of Line Orientation test. Based on these data and a collective sample size of 185 (PMD: $n=58$, NPMD: $n=127$), the average standardized difference between groups was -0.37 (standard error $=0.25$). Average effect sizes for spatial reasoning within studies ranged from -0.45 to $+0.14$.

6.2. Psychomotor speed and dexterity

Motor skill was assessed in three studies (Jeste, Basso, Schatzberg) with a collective sample size of 138 (PMD: $n=64$, NPMD: $n=74$) using the Grooved Pegboard Test, Trail Making Test, and WAIS-R Digit Symbol tests. The standardized differences between the psychotic depression group and the comparison groups ranged between -0.80 and -0.66 (average standardized difference $=-0.73$, standard error $=0.07$).

6.3. Attention

Four articles (Schatzberg, Jeste, Basso, Simpson) reported data on measures of attention derived from the WAIS-R Digit Span Forward and Backward, Digit Vigilance Time and Errors, and the Stroop Color-Word Test color-word and interference scores. Based on these 4 articles and a collective sample size of 231 (PMD: $n=88$, NPMD: $n=153$), the average standardized difference between the psychotic depression groups and the comparison groups was -0.39 (standard error $=0.43$). Average effect sizes within studies ranged from -1.16 to $+0.85$ when comparing groups on attention tasks.

6.4. Memory

Four studies (Schatzberg, Jeste, Basso, Simpson) reported data from neuropsychological tests or scales that assess memory. Results were used from WMS-R Visual Reproductions I and II, WMS-R Logical Memories I and II, California Verbal Learning Test Short Delay, Long Delay, and Recognition scores. For verbal memory, average effect sizes within studies ranged from

Table 3
Individual effect sizes included in the meta-analytic review

Study	Test	Domain	Effect size
Schatzberg et al. (2000)	Trail Making Test-A	Psychomotor Speed	−0.36
	Trail Making Test-B	Psychomotor Speed	−0.61
	WAIS-R Digit Symbol	Psychomotor Speed	−1.17
	WAIS-R Block Design	Visual-Spatial Skills	−0.45
	Stroop Color Word-color/word score	Attention	−1.06
	Paragraph Recall Test-Immediate	Memory	−1.35
	Paragraph Recall Test-Delayed	Memory	−1.32
	WMS-R Visual Reproduction I	Memory	−0.51
	WMS-R Visual Reproduction II	Memory	−0.49
Jeste et al. (1996)	story learning	Memory	−0.98
	figure learnng	Memory	−0.58
	Trail Making Test-A	Psychomotor Speed	−1.12
	Trail Making Test-B	Psychomotor Speed	−1.13
	WAIS-R Digit Symbol	Psychomotor Speed	−0.84
	Grooved Pegboard Test-dominant	Psychomotor Speed	−0.56
	Grooved Pegboard Test-nondominant	Psychomotor Speed	−1.03
	WAIS-R Digit Span	Attention	−1.35
	Digit Vigilance Test-time	Attention	−1.04
	Digit Vigilance Test-errors	Attention	−0.16
	story recall	Memory	−0.71
Basso and Bornstein (1999)	Controlled Oral Word Association Test	Executive Functioning	−0.94
	WMS-R Logical Memory I	Memory	−0.60
	WMS-R Logical Memory II	Memory	−0.65
	CA Verbal Learning Test-short delay	Memory	−0.80
	CA Verbal Learning Test-long delay	Memory	−0.75
	WAIS-R Block Design	Visual-Spatial Skills	+0.75
	Judgment of Line Orientation	Visual-Spatial Skills	−0.48
	WMS-R Visual Reproduction I	Memory	−0.76
	WMS-R Visual Reproduction II	Memory	−0.99
	Trail Making Test-A	Psychomotor Speed	−0.40
	Trail Making Test-B	Psychomotor Speed	−0.55
	WAIS-R Digit Span (forward)	Attention	−0.63
	WAIS-R Digit Span (backward)	Attention	−0.37
	WMS-R Visual Span (forward)	Attention	−0.20
	WMS-R Visual Span (backward)	Attention	−0.58
	Grooved Pegboard Test-dominant hand	Psychomotor Speed	−0.71
	Grooved Pegboard Test-nondominant hand	Psychomotor Speed	−0.61
Kim et al. (1999)	Wisconsin Card Sorting Test-persev. Errors	Executive Functioning	−0.76
	Wisconsin Card Sorting Test-completed categories	Executive Functioning	−0.85
Simpson et al. (1999)	Rey Auditory Verbal Learning Test-trial 5	Memory	−0.43
	Rey Auditory Verbal Learning Test-delayed	Memory	−0.43
	Controlled Oral Word Association Test	Executive Functioning	−0.58
	Wisconsin Card Sorting Test-completed categories	Executive Functioning	−0.34
	Wisconsin Card Sorting Test-% persev err	Executive Functioning	−0.76
	Wisconsin Card Sorting Test-total errors	Executive Functioning	−0.69
	WAIS-R Digit Symbol	Psychomotor Speed	−0.55
	Rey-Osterrieth Complex Figure-copy	Visual-Spatial Skills	−0.70
	Rey-Osterrieth Complex Figure-memory	Memory	−0.28
	Trail Making Test-A	Psychomotor Speed	−0.44
	Trail Making Test-B	Psychomotor Speed	−1.84

−0.81 to −0.43. The average standardized difference across studies for verbal memory was −0.68 (standard error = 0.09), approximately two-thirds of a standard deviation. For visual memory tests, average group differences within studies ranged from −0.28 to −0.88. Based on effect sizes from four studies, with a collective sample size of 231 (PMD: $n = 88$, NPMD: $n = 153$), the average standardized difference was −0.51 (standard error = 0.14).

6.5. *Executive functioning*

Assessment of executive functioning was conducted in two studies (Simpson, Kim) utilizing the Wisconsin Card Sort test. Average standardized group differences were −0.81 and −0.60 for the two studies. The average standardized difference across the studies was −0.71 (standard error = 0.11) The collective sample size was 107 (PMD: $n = 32$, NPMD: $n = 75$).

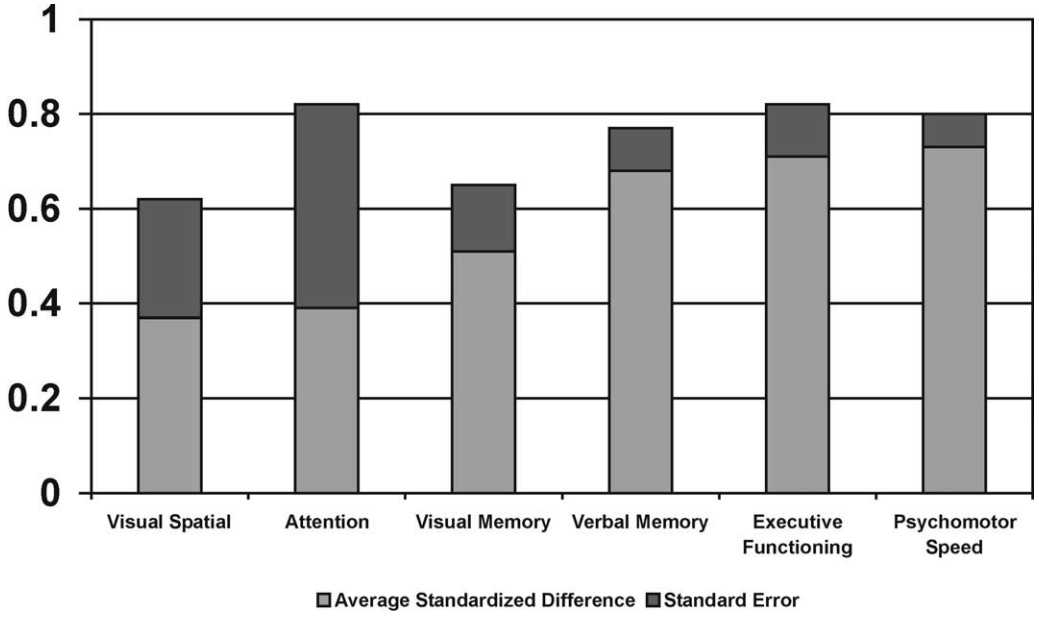

Fig. 2. Average standardized difference and standard error by neuropsychological domain.

7. Discussion

There are several limitations to the current meta-analytic review with the small number of available studies being the most obvious. Additionally, neuropsychological measures typically cannot provide precise localization of brain dysfunction in patients with psychiatric disorders. This lack of specificity also makes it very difficult to place some tests within only one cognitive domain. Further, because of the limited number of studies available, we chose to define our neuropsychological domains very broadly. Finally, limitations of test selection, subject selection, and other methodological factors (mixed medication status, mixed hospitalization status) cannot be controlled in a meta-analysis.

However, given the review process limitations, it is interesting to note that the largest standardized differences-and the smallest standard errors-are observed in the cognitive domains of verbal memory, executive functioning, and psychomotor speed. These processes are largely mediated by the hippocampus and prefrontal cortex. We cannot make more precise statements on localization of brain dysfunction, although these results are largely consistent with our hypothesis that HPA axis disruption may play a key role in the cognitive deficits observed in psychotic disorders, including PMD. However, the majority of neuropsychological tests reported were within the cognitive domains thought to be mediated by frontal and medial temporal brain regions, which may have artificially skewed the results toward our hypotheses.

Lupien (Lupien and Lepage, 2001) and Newcomer (Newcomer et al., 1994) have stressed different regions of interest in effects on cognition. Lupien's work has focused on the notion that HPA axis hyperactivity leads to decreased ability to perform cognitive tasks mediated by the prefrontal cortex, and represents a shift in the literature from Newcomer's more concentrated research on the hippocampus as the primary structure involved in these deficits. The results of the current meta-analysis and review suggest that we may ultimately require a more elaborate model accounting for the interactions between prefrontal and temporal structures given similar levels of deficit observed in executive processes and memory abilities (Schatzberg, 2002).

Regardless of the pathophysiological mechanism, there are clear neuropsychological differences that you can see that do track these anatomical regions whether cortisol is the determining factor or not. However, there is some evidence to suggest that cortisol does play a role in these results. Rothschild et al., (1989) reported larger ventricle-to-brain ratios, greater atrophy in parietal regions, and higher postdexamethasone cortisol levels in PMD patients compared to NPMD patients. These structural brain changes were also correlated with greater impairment on neuropsychological measures of motor function, attention, memory, and visual-spatial skills. Our ultimate goal is to capitalize on these differences in cognitive functioning as a means of facilitating differential diagnosis of PMD vs. NPMD in general clinical settings. While Nelson et al., (1998) was not included in the meta-analysis due to inability to calculate effect sizes from their data, this study provides an interesting finding of differential neuropsychological impairment on a computerized measure of sustained attention and concentration in psychotic vs. nonpsychotic patient

groups: normal controls, NPMD, PMD, and schizophrenia. Their results indicated normal functioning on this task in normal controls and NPMD. However, PMD and schizophrenia patients were significantly and equivalently impaired on this task. While Continuous Performance Test (CPT) deficits have been consistently reported in schizophrenia (Spaulding et al., 1996), this is the first such report in PMD. The apparent specificity with respect to nonpsychotic vs. psychotic patients is important as this task may reveal a marker for acute psychotic symptoms in the form of a specific attention deficit. We are currently investigating this hypothesis in our laboratory.

Jeste et al., (1996) also investigated neuropsychological functioning in NPMD, PMD, and schizophrenia. Further, their study likely reflects the best evidence of a single profile of impairment in PMD as they utilized a broad range of neuropsychological measures with scores corrected for both age and education. This study also illustrates the striking similarity of PMD to SCZ and the magnitude of the neuropsychological differences between PMD and NPMD (see Fig. 1) providing further support to the idea that PMD represents a distinct subtype of depression, and reinforcing our expectation that markers for the presence of psychotic features can be identified within the domain of neuropsychological functioning.

Finally, our review is suggestive of differences in cognitive domains that involve frontal and medial temporal regions of the brain. Deficits in prefrontal functioning could account for some portion of the observed memory deficits since it is difficult to construct a memory task that does not also involve some aspects of executive processing. However, our group is attempting to tease out the relative contributions of prefrontal and hippocampal dysfunction to the cognitive deficits associated with PMD in our ongoing studies. These studies will ultimately include analysis of sensitivity and specificity of neuropsychological deficits in PMD and NPMD to further our goal of identifying differential diagnostic tasks.

Acknowledgements

This work is supported in part by grants from the NIMH (RO1 MH 50604 and T-32 MH 19938), as well as from the National Academy of Neuropsychology and NARSAD.

Dr. Schatzberg has been a consultant to Eli Lilly, Janssen, and Corcept Therapeutics. He is also a cofounder of Corcept Therapeutics.

References

Antelman SM, Chiodo LA. Stress: its effects on interactions among biogenic amines and role in the induction and treatment of disease. In: Iverson LL, Snyder SH, editors. Handbook of psychopharmacology. New York: Plenum Press; 1984. p. 279–334.

Basso MR, Bornstein RA. Neuropsychological deficits in psychotic versus nonpsychotic unipolar depression. Neuropsychology 1999; 13:69–75.

Born J, Kern W, Fehm-Wolfsdorf G, Fehm H. Cortisol effects on attentional processes in man as indicated by event-related potentials. Psychophysiology 1987:286–92.

Breier A, Wolkowitz OM, Doran AR, Bellar S, Pickar D. Neurobiological effects of lumbar puncture stress in psychiatric patients and healthy volunteers. Psychiatry Research 1988;25:187–94.

Coryell W, Pfohl B, Zimmerman B. The clinical and neuroendocrine features of psychotic depression. Journal of Nervous and Mental Disease 1984;127:528–821.

Diorio D, Viau V, Meaney M. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. The Journal of Neuroscience 1993;13:3839–47.

Glass GV, McGaw B, Smith ML. Meta-analysis in social research. Beverly Hills, CA: Sage; 1981.

Grossman RG. The relationship between hormonal mediators and systemic hypermetabolism after severe head injury. Journal of Trauma 1993;34:806–16.

Jeste DV, Heaton SC, Paulsen JS, Ercoli L, Harris J, Heaton RK. Clinical and neuropsychological comparison of psychotic depression with nonpsychotic and depression and schizophrenia. American Journal of Psychiatry 1996;153:490–6.

Kim DK, Kim BL, Sohn SE, Lim SW, Na DG, Paik CH, et al. Candidate neuroanatomic substrates of psychosis in old-aged depression. Progress in Neuropsychopharmacology and Biological Psychiatry 1999;23:793–807.

Kolb K, Wishaw IQ. Fundamentals of human neuropsychology. New York: WH Freeman; 1996.

Lindley SE, Bengoechea TG, Schatzberg AF, Wong DL. Glucocorticoid effects on mesotelencephalic dopamine neurotransmission. Neuropsychopharmacology 1999;21:399–407.

Lupien SJ, Lepage M. Stress, memory, and the hippocampus: can't live with it, can't live without it. Behavioral Brain Research 2001; 127:137–58.

Lykouras E, Christodoulou GN, Malliaras D. Type and content of delusions in unipolar psychotic depression. Journal of Affective Disorders 1985;9:249–52.

Lyons DM, Lopez JM, Yang C, Schatzberg AF. Stress-level cortisol treatment impairs inhibitory control of behavior in monkeys. Journal of Neuroscience 2000;20:7816–21.

Mauri M, Sinforiani E, Bono G, Bignati F, Berselli ME, Attanasio R, Nappi G. Memory impairment in Cushing's disease. Acta Neurologia Scandinavica 1993;87:52–5.

McEwen BS, Sakai RR, Spencer RL. Adrenal steroid effects on the brain: versatile hormones with good and bad effects. In: Schulkin J, editor. Hormonally induces changes in mind and brain. San Diego: Academic Press; 1993.

Nelson EB, Kenji WS, Strakowski SM. Attentional performance in patients with psychotic and nonpsychotic major depression and schizophrenia. American Journal of Psychiatry 1998;155: 137–9.

Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. Glucocorticoid-induced impairment in declarative memory performance in adult humans. Journal of Neuroscience 1994;14:2047–53.

Patel PD, Lopez JF, Lyons DM, Burke S, Wallace M, Schatzberg AF. Glucocorticoid and mineralocorticoid receptor as RNA expression in squirrel monkey brain. Journal of Psychiatric Research 2000;34: 383–92.

Roose SP, Glassman AH, Walsh BT, Woodring S, Vital-Herne J. : Depression, delusions, and suicide. American Journal of Psychiatry 1983;140:1159–62.

Rothschild AJ, Benes F, Hebben N, Woods B, Luciana M, Bakanas E, Samson JA, Schatzberg AF. Relationships between brain CT scan

findings and cortisol in psychotic and nonpsychotic depressed patients. Biological Psychiatry 1989;26:565–75.

Sanchez MM, Young LJ, Plotsky PM, Insel TR. Distribution of corticosteroid receptors in the rhesus brain; relative absence of glucocorticoid receptors in the hippocampal formation. J Neurosci 2000; 20:4657–68.

Schatzberg AF. Major depression: causes or effects? Am J Psychiatry 2002;159:1077–9.

Schatzberg AF, Posener JA, DeBattista C, Kalehzan MB, Rothchild AJ, Shear PK. Neuropsychological deficits in psychotic versus nonpsychotic major depression and no mental illness. American Journal of Psychiatry 2000;157:1095–100.

Schatzberg AF, Rothchild AJ. The role of glucocorticoids and dopaminergic systems in delusional (psychotic) depression. Annals New York Academy of Sciences 1988;537:462–71.

Simpson S, Baldwin RC, Jackson A, Burns A. The differentiation of DSM III-R psychotic depression in later life from nonpsychotic depression: Comparisons of brain changes measured by multispectral analysis of magnetic resonance brain images, neuropsychological findings, and clinical features. Biolgical Psychiatry 1999;45: 193–204.

Spaulding WD, Reed D, Poland J, Storzbach D. Cognitive deficits in psychotic disorders. In: Cognitive rehabilitation and neuropsychiatric disorders. Washington, DC: American Psychiatric Press; 1996.

Spreen O, Strauss E. A compendium of neuropsychological tests. New York: Oxford University Press; 1998.

Varney NR, Alexander B, MacIndoe JH. Reversible steroid dementia in patients without steroid psychosis. American Journal of Psychiatry 1984;141:215–9.

Walker EF, DiForio C. Schizophrenia: a neural diathesis-stress model. Psychological Review 1997;104:667–85.

Wolf FM. Meta-analysis: quantitative methods for research synthesis. Beverly Hills, CA: Sage; 1986.

Wolkowitz OM, Doran A, Breier A, Cohen MR, Pickar D. Specificity of plasma HVA response to dexamethasone in psychotic depression. Psychiatry Research 1989;29:177–86.

Wolkowitz OM, Reus VI, Weingartner H, Thompson K, Breier A, Doran A, et al. Cognitive effects of corticosteroids. American Journal of Psychiatry 1990;147:1297–303.

Wolkowitz OM, Weingartner H, Rubinow DR, Jimerson D, Kling M, Berretini W, et al. Steroid modulation of human memory: Biochemical correlates. Biological Psychiatry 1993;33:744–6.