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General psychopathology is more important for executive functioning than diagnosis

Stordal KI, Mykletun A, Asbjørnsen A, Egeland J, Landrø NI, Roness A, Rund BR, Sundet KS, Lundervold AJ, Lund A. General psychopathology is more important for executive functioning than diagnosis.
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Objective: Impaired executive functioning (EF) has often been reported in patients with major depression or schizophrenia. We hypothesize that the variance in EF is more affected by level of general psychopathology than by diagnosis.
Method: Forty-three patients with major depression and 47 with schizophrenia were included. EF was measured with Wisconsin Card Sorting Test, Stroop Colour Word Test, Paced Auditory Serial Addition Test, Digits Backwards and Controlled Oral Word Association Test. The level of general psychopathology was measured with Brief Psychiatric Rating Scale – Expanded and Positive and Negative Syndrome Scale, the General psychopathology subscale.
Results: The level of general psychopathology predicted more of the variance in EF than diagnosis. In multivariate analyses, the effect of general psychopathology on EF was more robust for adjustment for diagnosis than vice versa.
Conclusion: Future research on cognitive functioning in psychiatric patients should include level of general psychopathology to avoid overemphasising effects of diagnoses.

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Key words: major depression; schizophrenia; cognitive functions; executive functions; general psychopathology

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Introduction

Most neuropsychological studies find impaired performance in patients with major depression or schizophrenia, with schizophrenic patients consistently performing at lower levels than patients with major depression (1–2). There is also an inter-individual variation in severity of cognitive impairment in both major depression and schizophrenia, with some patients performing in the impaired and some in the non-impaired range (3–4).

To our best knowledge there is yet no general understanding of a specific cognitive profile for major depression or schizophrenia, although several studies have compared the neuropsychological patterns of the two diagnostic groups (1, 2, 5–8). Cognitive impairment has nonetheless been suggested as a core feature in both major depression and schizophrenia; especially in schizophrenia (9, 10).

Major depression and schizophrenia can be characterized as heterogeneous disorders (11). The symptomatology, severity, course and prognosis of the disorders vary across patients. In addition, the clinical picture and thereby the diagnosis may change over time from, i.e. unipolar depression to bipolar disorder or from bipolar disorder to schizophrenia (1, 12). Also, co-morbid psychiatric diagnoses of schizophrenia and major depression are common (11). Yet another problem is that the diagnoses and the criteria for these are not absolute but based on consensus.

The diagnoses major depression and schizophrenia are not biologically real disease entities. The validity of the diagnostic classifications of today have therefore been questioned by findings from research on genetics, basic neurobiology and pathophysiology, and an improved classification based on such findings has been suggested (13, 14).

Impairment of executive functions (EF) has consistently been reported in both patients with major depression and schizophrenia (2, 6, 8, 9, 15–19). Executive functions can be defined as the

cognitive skills needed for purposeful, goal-directed activity (20), and can be regarded either as a general function or as several sub-functions which can be operationalized using specific neuropsychological tests (21). Executive functioning impairment is associated with frontal lobe dysfunction. In major depression, the EF impairment may be particularly prominent, although deficits are shown also in other cognitive domains (4, 6). Executive functioning impairment has also been reported in unmedicated depressed patients (3, 22). Nonetheless, there seems to be a heterogeneity of both EF impairment and severity in major depression (4, 18), and Stordal et al. found that more than half of a sample of patients with recurrent major depression were not EF impaired when moderately to severely depressed (personal communication). In schizophrenic patients, a reduced frontal activation (hypofrontality) has often been reported in activation state neuroimaging studies, a finding often reported also in patients with major depression (23, 24). Lately, a study showed that neuropsychological treatment increased prefrontal blood flow, gave higher performance on cognitive and especially EF tasks, and reduced negative symptoms (25). As for patients with major depression, the degree of EF impairment in schizophrenic patients varies across tasks and patients (8).

The dimensional or continuum hypothesis is old in psychiatry (11, 26). Today, because of recent findings in genetics and neuroscience, there is a growing interest for this hypothesis (13, 14). Lately, Möller (27) suggested a psychiatric continuum ranging from bipolar disorder to schizophrenia based on findings from genetic, biochemical and pharmacological studies. A recent review also hypothesized anxiety and depression as different expressions of a common neurobiological origin (28). And as mentioned above, some patients change diagnoses from unipolar depression to bipolar disorder over time and also to schizophrenia. Thus, major depression and schizophrenia can be viewed as different levels of psychopathology, sharing some of the same features (emotional, behavioural, cognitive and neuropsychological) but to different degrees.

Aims of the study

The aim of the present study was to examine if differences in EF between diagnostic groups (major depression vs. schizophrenia) merely can be attributed to differences in level of general psychopathology (LGP).

Material and methods

Subjects and clinical assessment

Forty-three depressed patients and 47 schizophrenic patients were included in the study. The subjects have previously been described elsewhere (5, 17). The patients were examined at five different psychiatric hospitals in Bergen and Oslo, Norway. They were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, version 2.0) (29). All the depressed subjects met DSM-IV diagnostic criteria for major depressive disorder, recurrent type, and the schizophrenic patients met DSM-IV diagnostic criteria for schizophrenia (30). There was one patient with catatonic type, three with disorganised type, 37 paranoid type, two residual type and four undifferentiated type. The depressed patients were moderately to severely depressed, according to the Hamilton Depression Rating Scale, 17-items (HDRS) (mean 22.2, SD 4.4, range 18–42) (31) and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Mean 28.6, SD 4.5, range 21–38) (32). The great majority of the depressed patients were on newer antidepressant medication (mainly SSRIs), and none were on tricyclic medication. In the schizophrenic group, the majority were on second generation atypical antipsychotic medication. The two groups were matched on level of education, whereas there were significant group-differences for age and gender (Table 1). The study was approved by the Regional Committee for Medical Ethics. All participants provided written informed consent to participate in the study.

Level of general psychopathology

The LGP can be viewed as a dimensional or continuum variable. LGP can be measured with, i.e. the Brief Psychiatric Rating Scale-Expanded (BPRS-E) (33) and the Positive And Negative Syndrome Scale, the General Psychopathology Subscale (PANSS-G) (34). In the present study, a composite score based on sum scores from both these scales were used, because both measures together gave higher effect sizes than each one alone in the statistical analyses. BPRS-E is widely used in the evaluation of level of symptoms in different psychiatric patient groups and also in schizophrenia and mood disorders. The PANSS was mainly developed to assess symptom levels in schizophrenic patients but has previously also been included in studies of depressed patients (35). For the included patients ($n = 90$), the results of the BPRS-E total and PANSS-G sum score had a normal distribution. Standardised scores (z-scores)

Table 1. Sample characteristics

Variable type	Variable	Depressed patients ($n = 43$) Mean	SD	Range	Schizophrenic patients ($n = 47$) Mean	SD	Range	*z*-difference	Significance
Sociodemographics	Age (years)	35.28	8.44	19–51	31.13	8.54	20–49	−0.48	0.023
	Gender (M/F)	16/27	–	–	31/16	–	–	–	0.006*
	Education (years)	13.84	2.73	9–19	13.43	3.11	9–24	−0.14	0.507
General psychopathology (LGP)	BPRS-E	43.16	6.60	29–70	51.64	17.28	24–96	0.61	0.003
	PANSS-G	32.58	4.92	23–42	37.66	18.83	14–65	0.57	0.006
	LGP summary score	−0.64	0.98	−2.77–1.94	0.56	2.45	−4.17–6.87	0.61	0.004
Executive functions (EF)	PASAT	79.21	24.28	24–118	62.40	28.66	1–117	−0.60	0.004
	DB	5.81	1.67	3–11	5.06	2.14	1–10	−0.38	0.069
	COWAT phonemic	23.98	7.57	6–45	21.98	8.03	7–41	−0.26	0.229
	COWAT categorical	40.27	10.11	22–62	33.66	8.45	19–55	−0.67	0.001
	FTMS	1.49	1.65	0–6	1.21	1.18	0–5	−0.19	0.362
	STROCW	54.37	12.97	33–85	61.45	24.20	16–141	0.36	0.092
	EF summary score	1.12	3.05	−5.53–6.69	−0.88	3.37	−7.79–6.38	−0.60	0.004

BPRS-E, Brief Psychiatric Rating Scale-Expanded version, total sumscore; PANSS-G, Positive and Negative Syndrome Scale, General psychopathology subscale, total sumscore; PASAT, Paced Auditory Serial Addition Test, sum of 3- and 2-s interstimulus intervals subtests; DB, Digit Span, backwards from WAIS-R; COWAT phonem, Controlled Oral Word Association Test, phonemic verbal fluency; COWAT categor, Controlled Oral Word Association Test, categorical verbal fluency; FTMS, Wisconsin Card Sorting Test, Failure to Maintain Set; STROCW, Stroop Colour Word Test, the colour-word subtask.
*Pearson's chi-square test $\chi^2 = 7.44$, or else student *t*-tests.

were then calculated for each of these measures. A Cronbach's coefficient alpha of 0.94 was found for the *z*-scores. The results from these scores were then summarized to obtain a LGP summary score.

Operationalization of EF

The neuropsychological assessment was performed within 3 days after the clinical psychiatric assessment. Each participant completed a set of neuropsychological tests, selected to assess central areas of EF. These tests were the Paced Auditory Serial Addition Test (PASAT) (36), the Digit Backward subtest (DB) from Wechslers Adult Intelligence Scale-Revised (37), the Controlled Oral Word Association Test (COWAT) (38), the Failure to Maintain Set variable from Wisconsin Card Sorting Test (WCST) (39) and the Colour-Word subtask from the Stroop Colour Word Test (Stroop) (40, 41). These five tests were used as measures of four different subcomponents or areas of EF. The PASAT measure (the sum of the 3- and the 2-s interstimulus interval subtests) and the DB measure were used to assess working memory. On the COWAT the phonemic (sum of letters F and A) and categorical verbal fluency (sum of categories animals and clothes) scores were added and this sum score was used as a measure of verbal fluency. The WCST score was used as a set-maintenance measure and the Stroop variable as an inhibition measure.

The results of the four EF subcomponents were normalized using power-transformation or dichotomization. Standardized scores (*z*-scores) were then calculated for the set-maintenance, inhibition, verbal fluency and working memory measure results for the depressed and schizophrenic patients together ($n = 90$). A Cronbach's coefficient alpha of 0.61 was found for the *z*-scores calculated from the four EF measures. The results from these scores were then summarized to obtain a single EF summary score.

Statistics

The SPSS for Windows 11.0.0 was used for statistical analyses. Multiple linear regression models were performed. In all models the standardized residuals were within ± 2 SD. No problem of multicolinearity was revealed when examining the tolerances (all tolerance coefficients > 0.3). A shared variance of 0.13 was found between diagnosis and BPRS-E, 0.08 between diagnosis and PANSS-G, and 0.09 between diagnosis and the composite LGP score. All presented results from regression analyses (hence Tables 2 and 3) are adjusted for age and gender, and results reported are statistically significant with two-tailed level of significance at $P < 0.05$.

Results

There were differences between the depression and schizophrenia groups for age and gender, whereas there were no group differences in education. There were group differences in BPRS-E, PANSS-G, and

Table 2. Explained variance in EF of diagnoses with vs. without adjustment for LGP

	Model 1 crude beta	Significance	Model 2 adjusted beta	Significance
EF summary score	−0.329	0.003	−0.248	0.019
Explained variance (R^2)	0.097	0.003	0.099	0.001

Model 1: Only diagnoses as predictor.
Model 2: Adjustment for LGP.

Table 3. Explained variance in EF of LGP with vs. without adjustment for diagnoses

	Model 1 crude beta	Significance	Model 2 adjusted beta	Significance
EF summary score	−0.396	0.000	−0.338	0.001
Explained variance (R^2)	0.144	0.001	0.052	0.019

Model 1: Only LGP as predictor.
Model 2: Adjustment for diagnoses.

the composite LGP measure as well as on PASAT, COWAT categorical verbal fluency, and on the composite EF measure. The ranges for BPRS-E and PANSS-G illustrate that there was an overlap between major depressed and schizophrenic patients on these rating scales.

LGP predicted more of the variance (14.4%) in EF than did diagnoses (9.7%) (left half of Tables 2 and 3, respectively). Correspondingly, the standardized regression coefficients (betas) were stronger in LGP than in diagnoses (−0.396 vs. −0.329).

Results from multivariate analyses are given in the right halves of Tables 2 and 3. LGP predicted only about 25% of the effect of diagnoses on EF, hence the drop in standardized regression coefficients of diagnosis on EF from −0.329 in the crude model to −0.248 when adjusted for LGP. In other words, most of the effect of diagnoses on EF could not be attributed to LGP.

Diagnoses predicted about 15% of the effect of LGP on EF, hence the drop in standardized regression coefficients of LGP on EF from −0.396 in the crude model to −0.338 when adjusted for diagnoses. Thus, most of the effect of LGP on EF could not be attributed to diagnoses.

In Table 2, it is shown that approximately 5% of the variance in EF could be predicted by diagnoses, when LGP was already included in the model.

In Table 3, it is shown that approximately 10% of the variance in EF could be predicted by LGP, when diagnosis was already included in the model.

To sum up, LGP has a stronger independent effect on EF and predicts more additional variance in EF in addition to diagnosis than vice versa.

Discussion

The results show that LGP predicts more of the variance in EF than DSM-IV diagnosis, but that diagnosis also has an independent contribution to EF. In other words, the effect of LGP can partially be attributed to diagnosis, and the effect of diagnosis on EF can also partially be attributed to LGP, but the effect of LGP seems somewhat more robust. Thus, both LGP and diagnosis contribute with independent explanations to the variance in EF.

To our best knowledge, this is the first study to describe that LGP is a stronger predictor of EF than diagnosis in psychiatric patients. It seems that the variance in EF cannot be viewed merely as a function of diagnosis. In the present study, we mixed patients with major depression and schizophrenia in order to achieve a greater variance in psychiatric symptoms than by studying each diagnostic group alone. It is probably also the first study to handle both psychopathology and cognitive performance (EF) as dimensional measures.

Several prior studies have compared the performance of patients with major depression and schizophrenia on neuropsychological tests. Most authors have reported quantitative differences between the groups (1, 7, 8), whereas some have argued that there are qualitative differences or specific cognitive profiles for the two diagnostic groups (1). Possible associations between cognitive performance and psychopathology have also been studied in both depression and schizophrenia separately. In depressed patients, Merriam et al. (2) found a correlation between some WCST measures and severity of depression as measured by HDRS, whereas Degl'Innocenti et al. (18) and Fossati et al. (8) found the performance across EF tasks to be unrelated to severity of depression as determined by hence HDRS and MADRS. In schizophrenia, no correlation was found between performance on EF tests and ratings from the PANSS (8) but a significant correlation has been reported between negative symptoms and WCST in a recent meta-analysis (42). Thus, within each diagnostic category it is still unclear whether an association between illness severity and cognition exists, and it has been argued that psychiatric symptoms and cognitive deficits seem to be relative independent disease processes (42).

In contrast, our study investigated associations between cognitive performance and psychopathology within a group containing a mixture of psychiatric patients with overlapping levels of psychopathology (with some major depressed

patients having greater symptom load than some schizophrenic patients). Therefore, there was probably also a larger variance in psychopathology than when investigating such an association within a single diagnostic group. A dimensional variable (LGP) might be better in explaining the variance in EFs and may be also in other cognitive functions. The results of this study is thus in line with both quantitative and qualitative explanations. It could be argued that the results even are stronger because of the fact that patient groups studied were homogeneous; they did not contain patients with intermediate diagnoses such as schizoaffective disorder, bipolar disorder or psychotic depression.

Cognitive impairment, and especially EF impairment have been reported also in other diseases, i.e. lung cancer, dementia and alcoholism (43–45). May be, the EF impairment is an expression of a common underlying mechanism when ill. Others could claim that this is because of the fact that EF is not a specific deficit, and if one should search for a cognitive dimension where degree of psychopathology would predicts more than kind of pathology, EF would be a good candidate. The study should therefore be replicated and the hypothesis tested on also other cognitive domains or on a general cognition measure.

The results can in part be taken as support for the continuum hypothesis, regarding schizophrenia and major depression as two states along a psychiatric continuum. However, since diagnosis also contribute independently, there must be some characteristics that are specific for the two diagnoses.

Much of the neuropsychological research today is engaged in finding specific profiles for certain diagnostic groups of psychiatric patients, but the results are conflicting as exemplified by the unclear association between clinical measures and cognitive performance or the cognitive patterns that seems to differ across studies. Some authors have attributed these inter-study differences to different tests used and patient samples studied (6, 9). In a neuropsychological study by Zihl et al. (46), patients with schizophrenia and affective disorders could not be qualitatively distinguished with sufficient reliability and the authors argued a final common pathway disorder in the two groups of patients. In this paper, attention deficits was suggested as the most likely cause of cognitive disorders in both groups; a deficit that 'can be caused by any type of disturbance of the underlying network, whereby subtypes of deficit patterns may reflect regional differences in involvement within the network' (46). As a parallel, the same could be argued for EF impairment, because any disturbance along the frontal-subcortical system can result in EF impairment.

Genetic researchers within psychiatry have been critical to our existing diagnostic classification systems. In one paper, it was formulated like 'the current classification schema in psychiatry were derived from observable clinical grounds to address the need for clinical description and communication' but that 'the lack of a biological basis for the classification of psychiatric disorders has led, in part to a lack of success in studies of the neurobiology and genetics of psychiatric disorders' (47). May be, it has also lead to a lack of success within the field of neuropsychiatry. In future neuropsychological research, we think one should look beyond the classic psychiatric diagnoses and study more heterogeneous groups in order to find out more about underlying psychopathology and real biological disease entities. In addition, the fact that depression frequently co-occur with other psychiatric syndromes and also with a range of medical diseases, points to a need to 'integrate spectrum and dimensional approaches in addition to categorical diagnostic ones' (48). Neuropsychology could be one method used to get more insight, especially when combined with other methods such as neuroimaging, genetics, biochemistry and neurophysiology.

To conclude, our results imply the importance of viewing both EF and psychiatric illnesses as dimensional measures. Executive functions have been shown to be essential for complex activities of daily living (49), and impairment may have a large impact on the lives of patients with major depression and schizophrenia. It is therefore important to find out more about these cognitive functions. The study has only illustrated a way of thinking by numbers, and therefore the results need to be replicated. Nonetheless, future research on cognitive functioning in psychiatric patients should include a measure of the LGP in empirical models (in addition to diagnoses) to avoid overemphasising effects of diagnoses.

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