Long-term functioning in major psychiatric disorders and its clinical and psychosocial predictors: a potential cross-diagnostic phenotype for further genetic investigations?

Gade K[1], Malzahn D[2], Strohmaier J[3], Frank J[3], Meier S[3], Treutlein J[3], Witt S[3], Anderson-Schmidt H[1], Budde M[1], Heilbronner U[1], Reitt M[1], Rietschel M[3],Schulze TG[1]

[1]Dept. of Psychiatry and Psychotherapy, University Medical Center, Georg-August-University Göttingen, Germany
[2]Dept. of Genetic Epidemiology, University Medical Center, Georg-August-University Göttingen, Germany
[3]Dept. of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany

Background

Large parts of the heritabilities of psychiatric disorders have not yet been accounted for by the genomic findings of the last decade. This may in part be due to the difficulty of defining specific phenotypes. At times, it is not easy to clinically distinguish between these disorders as symptoms often overlap and vary widely during the course of illness. Therefore, researchers have attempted to identify better-defined subphenotypes sharing certain phenotypic similarities across diagnostic boundaries, as these overlaps may be due to a common genetic basis. Here we study global functioning as a potential cross-diagnostic phenotype. Long-term global functioning – as measured by the Global Assessment of functioning score (GAF, Endicott et al.1976) – was assessed in patients with schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD). We compared the predictive value of several clinical and psychosocial variables for functional outcome between these disorders and discuss the relevance of our findings for further genetic investigations.

Methods

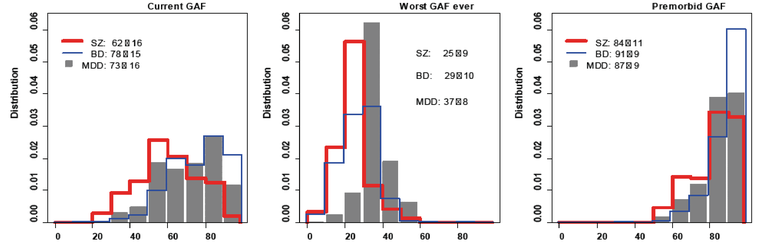
Based on a structured interview (SCID-I for DSM-IV) and a review of clinical records using lifetime ratings of the Operational Criteria Checklist (OPCRIT, First et al. 1994), we assessed several sociodemographic and clinical variables in inpatients with DSM-IV-diagnoses of SZ (n=238), BD (n=533), and MDD (n=398). For each patient, we determined global functioning (GAF) at three points in time over the course of illness: premorbid GAF (GAF1), worst GAF-score during course of illness (GAF 2) and current GAF directly before the disease episode for which the patient received clinical treatment (GAF 3). GAF 3 was analyzed as outcome parameter for long-term functioning, and the predictive value of clinical and sociodemographic variables was determined.

Results

Different functioning levels in SZ,BD and MDD

As expected, the distribution and the mean levels of premorbid functioning, current functioning and the extent of functional impairment during the course of illness differed between the disorder groups (figure 1).

Figure 1



Distribution of GAF values for SZ (red), BD (blue), MDD (grey) with respective mean and standard deviation (SD). From left to right: current GAF (GAF3), worst ever GAF (GAF2) and premorbid GAF (GAF1).

Shared and disorder-specific predictors of functional outcome

An overview of shared and disorder-specific predictors of functional outcome in the three disorders is shown in figure 2, detailed statistics are shown in table 1.

A linear regression model revealed low premorbid functioning, poor premorbid work/social adjustment, and insidious illness onset to be significantly associated with worse functional outcome in all three disorders. Additionally, lifetime occurrence of negative symptoms predicted worse functional outcome in BD and SZ patients. However, levels of functioning were also found to be disorder-specifically influenced by other factors, which differed according to diagnostic group. For SZ patients, longer duration of illness and lower levels of global functioning during episodes were found to have a major impact on long-term functioning, whereas for BD patients lifetime substance abuse and lifetime occurrence of suicidality were important predictors for worse functional outcome. A premorbid personality disorder and unemployment at illness onset appeared to negatively influence long-term functioning in MDD. Figure 3 depicts the different extent to which the predictive variables contribute to worse functional outcome in the three disorders via the explained variability of current GAF for each predictor.

In an additional explorative analysis, the following disorder-specific combinations of variables were identified by stepwise regression to jointly predict functional outcome in each of the three entities (table 2). In SZ patients, the model included poor premorbid social adjustment, longer duration of illness, negative symptomatology, and lifetime single status (in total accounting for 28% of the observed variance of functional outcome). In BD patients, premorbid level of functioning, negative symptomatology, lifetime cannabis and other drug abuse accounted for 22% of the trait variance. In MDD patients, the premorbid level of functioning alone was found to predict long-term functioning in a univariate model, accounting for 26 % of the trait variance.

Table 1:

Association with current GAF in SZ (N=238), BD (N=533), MDD (N=398)

PRIMARY ANALYSIS	Group	Median [Interquartile]	R^2_{adj} (%)	INFLUENCE ON CURRENT GAF: Effect [98.33% CI]	t-statistic	P value
GAF1 Premorbid GAF	SZ	86 [80-91]	***11.6***	0.5 [0.3 , 0.7]	t_{536}= 5.665	***4.3×10⁻⁸***
	BD	91 [90-98]	***18.2***	0.7 [0.6 , 0.9]	t_{531}=10.932	***<2×10⁻¹⁶***
	MDD	90 [81-91]	***25.6***	0.9 [0.7 , 1.1]	t_{395}=11.743	***<2×10⁻¹⁶***
GAF2 Worst GAF ever	SZ	25 [20-30]	***5.3***	0.4 [0.2 , 0.7]	t_{536}= 3.780	***2.0×10⁻⁴***
	BD	30 [21-35]	0.2	0.09 [-0.07, 0.2]	t_{531}= 1.342	0.18
	MDD	35 [31-41]	0	-0.06 [-0.3 , 0.2]	t_{395}= -0.605	0.55
Age (years)	SZ	34 [27-41]	0.4	-0.1 [-0.4 , 0.09]	t_{536}= -1.422	0.16
	BD	46 [37-56]	0	0.009 [-0.1 , 0.1]	t_{531}= 0.184	0.85
	MDD	47 [37-57]	1.1	0.1 [-0.005, 0.3]	t_{395}= 2.328	$2.0×10^{-2}$
Duration of illness[a] (years)	SZ	6 [2-13]	3.6	-0.4 [-0.7 , -0.08]	t_{351}= -3.073	$2.4×10^{-3}$
	BD	16 [7-25]	0.2	-0.07 [-0.2 , 0.05]	t_{514}= -1.400	0.16
	MDD	8 [2-17]	0.04	0.08 [-0.1 , 0.3]	t_{392}= 1.083	0.28
OPCRIT-ITEMS						
3 Sex (female)	SZ	39%	2.2	5.4 [0.2 ,10.6]	t_{534}= 2.497	$1.3×10^{-2}$
	BD	55%	0	0.5 [-2.6 , 3.7]	t_{527}= 0.403	0.69
	MDD	65%	0	-1.6 [-5.6 , 2.4]	t_{395}= -0.985	0.33
4 Age of onset (years)	SZ	24 [20-31]	1.6	0.3 [-0.04, 0.6]	t_{227}= 2.145	$3.3×10^{-2}$
	BD	25 [20-36]	0.3	0.09 [-0.05, 0.2]	t_{516}= 1.549	0.12
	MDD	35 [27-45]	0.5	0.1 [-0.04, 0.3]	t_{392}= 1.725	0.085
5 Mode of onset						
moderately acute	SZ	25%	***8.4***	-5.7 [-13.3, 1.8]	t_{223}= -1.832	0.068
gradual	SZ	20%		-10.1 [-18.1,-2.2]	t_{223}= -3.089	$2.3×10^{-3}$
insidious	SZ	35%		-13.5 [-20.6,-6.5]	t_{223}= -4.623	***6.4×10⁻⁶***
moderately acute	BD	24%	***2.0***	-3.5 [-7.7, 0.7]	t_{506}= -1.998	$4.6×10^{-2}$
gradual	BD	19%		-2.6 [-7.1, 1.9]	t_{506}= -1.398	0.16
insidious	BD	23%		-6.4 [-10.7,-2.1]	t_{506}= -3.593	***3.6×10⁻⁴***
moderately acute	MDD	35%	***5.9***	-0.3 [-6.0, 5.4]	t_{171}= -0.121	0.90
gradual	MDD	26%		-1.2 [-7.2, 4.9]	t_{171}= -0.460	0.65
insidious	MDD	23%		-10.1 [-16.2,-3.9]	t_{171}= -3.944	***9.6×10⁻⁵***
6 Lifetime single	SZ	64%	2.8	-6.1 [-11.4,-0.8]	t_{532}= -2.788	$5.8×10^{-3}$
	BD	30%	0	-0.9 [-4.3, 2.5]	t_{524}= -0.656	0.51
	MDD	21%	0.7	-3.9 [-8.6, 0.8]	t_{395}= -1.981	$4.8×10^{-2}$
7 Unemployment at onset	SZ	30%	1.7	-5.1 [-10.7, 0.5]	t_{221}= -2.197	$2.9×10^{-2}$
	BD	16%	1.0	-4.6 [-8.8, -0.3]	t_{221}= -2.550	$1.1×10^{-2}$
	MDD	10%	***3.1***	-9.7 [-16.1, -3.3]	t_{395}= -3.668	***2.8×10⁻⁴***
9 Poor premorbid work adjustment	SZ	27%	***15.3***	-14.4 [-19.8, -9.1]	t_{228}= -6.488	***5.4×10⁻¹⁰***
	BD	5%	***3.3***	-12.6 [-19.5, -5.6]	t_{514}= -4.341	***1.7×10⁻⁵***
	MDD	3%	***3.0***	-15.7 [-26.2, -5.2]	t_{395}= -3.607	***3.5×10⁻⁴***
10 Poor premorbid social adjustment	SZ	29%	***17.6***	-15.3 [-20.6,-10.0]	t_{223}= -6.995	***3.1×10⁻¹¹***
	BD	7%	***3.2***	-11.1 [-17.3, -4.8]	t_{514}= -4.250	***2.5×10⁻⁵***
	MDD	5%	***6.1***	-17.5 [-25.8, -9.3]	t_{395}= -5.119	***4.8×10⁻⁷***
11 Premorbid personality disorder	SZ	7%	2.2	-10.3 [-20.4,-0.2]	t_{219}= -2.450	$1.5×10^{-2}$
	BD	3%	0.8	-9.0 [-18.4, 0.5]	t_{484}= -2.285	$2.3×10^{-2}$
	MDD	2%	2.4	-17.0 [-29.6,-4.4]	t_{385}= -3.251	$1.3×10^{-3}$
29, 32, 33 Negative Symptomatology	SZ	72%	***9.7***	-11.5 [-17.0,-6.0]	t_{228}= -5.089	***8.2×10⁻⁷***
	BD	46%	***2.6***	-5.0 [-8.1, -1.9]	t_{514}= -3.862	***1.3×10⁻⁴***
	MDD	19%	0	-1.2 [-6.0, 3.7]	t_{395}= -0.575	0.57
43 Suicidal ideation	SZ	65%	0	-0.8 [-6.3, 4.7]	t_{228}= -0.339	0.74
	BD	76%	1.7	-4.8 [-8.4,-1.1]	t_{523}= -3.150	$1.7×10^{-3}$
	MDD	76%	0.9	-3.9 [-8.3, 0.6]	t_{395}= -2.101	$3.6×10^{-2}$
52 Affective symptoms 54, 55, 57-76 Psychotic symptoms	SZ	78%	0	-1.1 [-7.9, 5.6]	t_{195}= -0.401	0.69
	BD	62%	0	-0.7 [-3.9, 2.5]	t_{521}= -0.519	0.60
	MDD	10%	0	0.5 [-5.7, 6.8]	t_{391}= 0.210	0.83
78, 79, 80 Lifetime substance abuse	SZ	36%	0	-1.3 [-6.7, 4.1]	t_{230}= -0.565	0.57
	BD	24%	***3.9***	-7.0 [-10.6,-3.4]	t_{520}= -4.690	***3.5×10⁻⁶***
	MDD	19%	0.2	-2.8 [7.7, 2.1]	t_{395}= -1.358	0.18

Proportion of explained variability (adjusted R2) of current GAF and difference of group means or regression coefficient (with 98.33% confidence limits (CI), t-statistic tdf with df degrees of freedom, p value). Bonferroni adjustment for multiple testing (over all disease cohorts: p≤0.05/(3*18) bold, for single cohort: p≤0.05/18 italic)
Abbreviations: GAF, global assessment of functioning; N, samplesize.

Table 1b:

Association with current GAF in SZ (N=238), BD (N=533), MDD (N=398)

SECONDARY ANALYSIS of Item SUBSTANCE ABUSE	Group	%	R^2_{adj} (%)	INFLUENCE ON CURRENT GAF: Effect [98.33% CI]	t-statistic	p value
OPCRIT-ITEMS						
78 Lifetime alcohol abuse	SZ	24%	0.1	-2.8 [-8.9, 3.2]	t_{524}= -1.125	0.26
	BD	20%	2.7	-6.3 [-10.1, -2.4]	t_{521}= -3.925	***9.8×10⁻⁵***
	MDD	14%	0	-2.0 [-7.5, 3.6]	t_{395}= -0.846	0.40
79 Lifetime cannabis abuse	SZ	21%	0	0.2 [-6.2, 6.6]	t_{228}= 0.073	0.94
	BD	6%	3.2	-11.6 [-18.1, -5.0]	t_{520}= -4.242	***2.6×10⁻⁵***
	MDD	2%	0	2.3 [-10.5, 15.1]	t_{395}= 0.427	0.67
80 Lifetime other substance abuse	SZ	11%	0	-1.2 [-9.6, 7.2]	t_{227}= -0.351	0.73
	BD	6%	3.1	-11.6 [-18.3, -5.0]	t_{521}= -4.205	***3.1×10⁻⁵***
	MDD	5%	1.2	-8.7 [-17.4, -0.1]	t_{395}= -2.431	$1.6×10^{-2}$

Proportion of explained variability (adjusted R^2) of current GAF and difference of group means (with 98.33% confidence limits (CI), t-statistic t_{df} with df degrees of freedom, p value). Multiple testing adjusted significances are set in bold.

Table 2:

Multiple models for prediction of long-term functioning in SZ, BD and MDD

Model[a]	Effect [95% CI]	t-statistic	p value
Schizophrenia (N=238):	***R^2_{adj}= 28.0%***		
Poor premorbid social adjustment	-11.7 [-16.1, -7.4]	t_{208}= -5.304	$2.9×10^{-7}$
Duration of illness (year)	-0.5 [-0.7, -0.2]	t_{208}= -3.968	$1.0×10^{-4}$
Negative symptomatology	-8.3 [-12.5, -4.0]	t_{208}= -3.834	$1.7×10^{-4}$
Single status	-4.8 [-9.0, -0.7]	t_{208}= -2.278	$2.4×10^{-2}$
Bipolar Disorder (N=533):	***R^2_{adj}= 22.1%***		
Premorbid GAF	0.7 [0.5, 0.8]	t_{511}= 9.976	$<2×10^{-16}$
Negative symptomatology	-4.4 [-6.7, -2.1]	t_{511}= -3.759	$1.9×10^{-4}$
Lifetime cannabis	-5.9 [-11.0, -0.9]	t_{511}= -2.335	$2.0×10^{-2}$
Lifetime other abuse	-5.1 [-10.2, -0.02]	t_{511}= -1.974	$4.9×10^{-2}$
Major Depressive Disorder (N=398):	***R^2_{adj}= 25.6%***		
Premorbid GAF	0.9 [0.7, 1.0]	t_{396}=11.743	$<2×10^{-16}$

[a]The best model to predict current GAF was determined per disease cohort by stepwise linear regression selecting predictors from 18 variables (worst ever GAF, premorbid GAF, current age, duration of illness, sex, age of onset, mode of onset, lifetime single, unemployed at onset, poor premorbid work adjustment, poor premorbid social adjustment, premorbid personality disorder, negative symptomatology, suicidal ideation, psychotic symptoms (for BD, MDD), affective symptoms (for SZ), lifetime abuse of alcohol, cannabis, or other substances). The models are linear in all variables. Displayed are the mutually adjusted effect sizes on current GAF (difference of group means or regression coefficient, t-statistic t_{df} with df degrees of freedom, p value) and the overall proportion of explained variability of current GAF (adjusted R^2).

Figure 2:

Shared and disorder-specific predictors of long-term global functioning

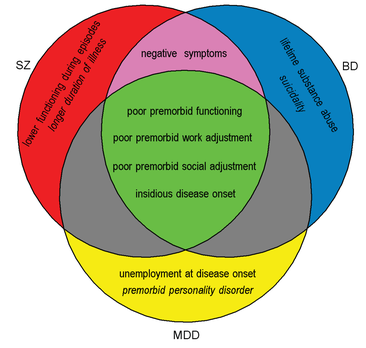
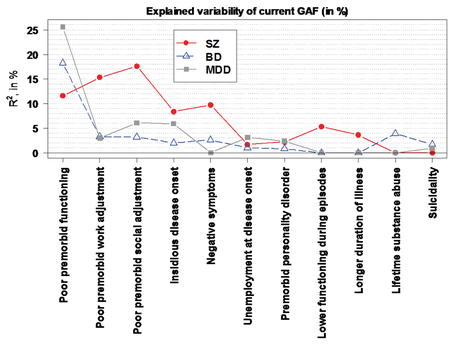


Figure 3



Discussion

Long-term global functioning may be an important phenotype for genetic studies. However, it is possibly difficult to use as a sole phenotype for cross-diagnostic investigations, as long-term functioning varies between SZ, BD and MDD. Furthermore, it seems to be influenced by several factors to a different extent in the three disorders.

Based on the findings of our investigation, the following points should be kept in mind when using long-term global functioning (or functional outcome) as a phenotype for genetic studies:

1. Some clinical and social variables appear to predict worse functional outcome in SZ as well as in BD and MDD. These variables (poor premorbid functioning, poor premorbid work and social adjustment, insidious disease onset, and in BD and SZ negative symptomatology) have previously been associated with a chronic course of illness especially in SZ, resulting in persistent and severe functional impairment (Kelley et al.1992). Therefore, it could be worth investigating whether having one or more of these clinical and psychosocial characteristics defines a cross-diagnostic subgroup of patients sharing a similar set of genetic factors. However, looking at the results of our explorative model, the variable expected to yield most genetic information across diagnostic boundaries might be the occurrence of negative symptoms in BD and SZ. It is on the list of most important predictors in both groups and could therefore indeed be used as a “proxy” for functional outcome when jointly analysing these two disorders.
2. Only in SZ the duration of illness had a significant negative impact on functional outcome. Hence, when using global functioning as outcome parameter in SZ, only patients with a similar duration of illness should be included into the analysis, or the analysis needs to be adjusted for duration of illness.
3. Compared to SZ and MDD, the influence of substance abuse in BD appears to be more important for functional outcome than many other clinical and psychosocial factors. Thus patients with substance abuse should be analyzed seperately when using global functioning for genetic investigations in BD.
4. In MDD, the premorbid level of functioning alone was found to be the most significant predictor accounting for 25 % of the variance of long-term functioning, while other variables seemed to add only minor additional predictive value. As MDD is an even more heterogeneous entity than SZ and BD, the relationship between premorbid and long-term functioning especially in this group of patients remains unclear. Before using long-term global functioning or its predictor premorbid functioning as outcome parameter for genetic analyses in MDD, further investigations seem to be needed to define clinical subphenotypes.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (grant Klinische Forschergruppe (KFO) 241: TP1 (SCHU 1603/5-1) and TP5 (BI 576/5-1).

Corresponding author:
Dr. Katrin Gade
CRG 241 / Psychiatric Genetics, University Medical Center Göttingen
E-mail: katrin.gade@med.uni-goettingen.de

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

References

Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976; 33(6): 766-771

First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for Axis I DSM–IV Disorders. 1994. New York: Biometrics Research.

Kelley ME, Gilbertson M, Mouton A, van Kammen DP. Deterioration in premorbid functioning in schizophrenia: a developmental model of negative symptoms in drug-free patients. Am J Psychiatry 1992; 149(11): 1543-8