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Flat Affect in Schizophrenia: Relation to Emotion Processing and Neurocognitive Measures

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Impaired emotional functioning in schizophrenia is a prominent clinical feature that manifests primarily as flat affect. Studies have examined the perception, experience, and expression of emotions in schizophrenia and reported normal ratings of experience but impaired affect identification. However, the relation between flat affect and performance on facial affect identification and cognitive tasks has not been systematically examined in relation to premorbid adjustment and clinical outcome. We report a prospective study of 63 patients with at least moderate severity of flat affect and 99 patients without flat affect, who were compared on functional domains, emotion processing tasks, and neurocognitive measures. Flat affect was more common in men and was associated with poorer premorbid adjustment, worse current quality of life, and worse outcome at 1-year follow-up. Patients overall performed more poorly on emotion processing tasks, one that required identification of happy and sad emotions and one that required differentiating among intensities within these emotions. They responded inaccurately yet faster than controls for the intensity differentiation task, suggesting a decomposition of the normal relation between accuracy and speed. Flat affect ratings, compared with other negative symptoms, uniquely predicted performance on emotion processing tasks. Patients with flat affect showed greater impairment in both emotion processing tasks, with the most pronounced impairment for the intensity differentiation task. However, the 2 patient groups did not differ in the neurocognitive profile except for verbal memory. We conclude that flat affect is an important clinical feature of schizophrenia that exacerbates the course of illness.

Key words: schizophrenia/flat affect/emotion processing/cognition

Introduction

Impaired emotional functioning is fundamental to schizophrenia,[1,2] and negative symptoms, including flat affect, are debilitating and resistant to intervention.[3] Studies of first-episode patients demonstrate that flat affect is present at the onset of illness[4] and is more evident in men than in women.[5–7]

Flat affect, assessed clinically based on emotional expressivity, has also been reported in laboratory studies with reduced facial expression during social interactions,[8] emotional films,[9,10] and cartoons.[11] Impaired performance was noted in affect perception tasks, including facial expression recognition, facial identity recognition, and unfamiliar face matching.[12–22] In contrast to reduced expressiveness and deficits in perception, reported emotional experience in schizophrenia appears normal across a range of evocative stimuli.[9,10] This suggests dissociation between reported experience of emotion and its display.[23,24]

There is limited knowledge on the relation between affective dysfunction and performance on emotion processing tasks.[25] Patients with blunted affect were not more impaired than nonblunted patients in the perception of emotions and self-report of the intensity of emotional experienece.[26] Other studies have correlated severity of negative symptoms with measures of emotion processing using facial[27] or auditory stimuli.[28] There is no data on adequately powered, well-characterized samples comparing patients with and without flat affect on emotion processing tasks.

Studies comparing emotion processing with cognitive performance measures have addressed primarily the issue of differential deficit.[29] In addition, studies have examined the relation between performance on emotion processing and neuropsychological measures. No association was found between ratings of flat affect and facial expression and tasks tapping right hemisphere or frontal lobe function.[30] However, relations were reported between performance on emotion discrimination and abstraction, memory, language, and spatial tasks.[18]

Our research aims to further delineate emotion processing deficits in schizophrenia. We developed procedures for examining emotion processing applying discrimination[31] and experience[32] probes. Patients were

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impaired in emotion discrimination[16,18,20,33–35] and had diminished response to mood induction, especially happiness.[36] The goal of the present study was to compare patients with schizophrenia with flat affect with those without flat affect in three domains: clinical, emotion processing, and neurocognitive. Based on previous findings, we hypothesized that flat affect is more common in men[6] and, as a negative symptom, portends poorer social functioning and worse quality of life.[4] Our main hypothesis was that flat affect is associated with poorer performance on emotion processing tasks. Within the broader domain of emotion identification, one can differentiate detection of the identity of an emotion from the ability to discriminate the intensity of expression. Our tasks were designed to measure emotion discrimination (Penn Emotion Acuity Test; PEAT) and the ability to depict subtle differences in intensity within emotions (Emotion Intensity Differentiation; Emodiff). Since the ability to distinguish among emotions (PEAT) is a prerequisite for distinguishing intensities of expressions within emotions (Emodiff), we expected that patients would be more impaired in the latter. Accuracy and speed are two complementary aspects of performance that are typically traded off.[37,38] As task difficulty is increased, an individual can either maintain accuracy by sacrificing speed or maintain speed at the expense of accuracy. However, when accuracy is constrained by impaired capacity to perform, a decomposition of speed and accuracy may occur in the direction of enhanced speed (''giving up'' response). We expected such a decomposition in patients with flat affect for the Emodiff task relative to the PEAT. Finally, because of the common limbic substrate for emotion processing and memory,[39,40] we also hypothesized that when comparing neurocognitive performance profiles, patients with flat affect are differentially impaired in memory.

Method

Participants

The sample consisted of 162 patients with schizophrenia (age range: 18–45) who were recruited and assessed by the Schizophrenia Research Center (SRC) and who received assessment of both cognitive and emotion processing measures. Patients underwent medical, neurological, and psychiatric evaluations to exclude for other history of illness affecting brain function, including substance abuse, hypertension, metabolic disorders, neurological disorders, and head trauma with loss of consciousness.[41] The comprehensive intake evaluation included a clinical interview, structured diagnostic interview,[42] and a review of records and information available from family and care providers that contributed to a consensus diagnosis of schizophrenia.[43] The clinical examination included assessment of symptoms and function, performed by trained, reliable (ICC $>$ 0.90) investigators.[41] Patients had mild to moderate symptoms at the time of study, as evaluated with the Scale for Assessment of Negative Symptoms (SANS[44]) 1.7 ± 1.1 and Scale for Assessment of Positive Symptoms (SAPS[45]) 1.5 ± 0.9. Onset of illness was defined as emergence of symptoms in the context of functional decline. Level of functioning was assessed with the Premorbid Adjustment Scale (PAS[46]) and the Quality of Life (QOL) Scale.[47] Patients were followed longitudinally, and 1-year outcome was assessed with the Strauss-Carpenter Outcome Scale (LEV).[48] Duration of illness, defined as age at study minus age of onset, was (mean ± SD) 8.6 ± 7.8 years. The sample consisted of 65 inpatients and 97 outpatients.

The healthy comparison sample for the neurocognitive and emotion processing tasks consisted of 138 healthy volunteers (age range: 18–45) recruited and assessed by the SCR with established procedures.[49] They underwent the same assessment procedures as patients, including the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition (SCID-NP),[50] and reported no first-degree relative with schizophrenia or affective illness. Patients and controls were balanced for age (patients 31.2 ± 9.1; controls 29.8 ± 7.9; t = 1.20, df = 298, p = .321), and while patients attained lower education as expected (patients 12.9 ± 2.3; controls 15.1 ± 2.2; t = 7.10, df = 298, $p < .0001$), the groups did not differ in parental education (patients 13.9 ± 3.1; controls 14.6 ± 2.8; t = 1.56, df = 298, p = .119).

All protocols were approved by the University of Pennsylvania institutional review board and were consistent with the principles outlined in the Helsinki guidelines for ethical conduct of human research. The study was performed after written informed consent was obtained.

Patients were divided into 2 groups based on the SANS score for flat affect, defined as a global rating ≥ 3 (3 = moderately severe) on the affective flattening subscale. There were 63 patients in the Flat Affect (FA) group (47 men and 16 women) and 99 patients in the Non-Flat Affect (NFA) group (56 men and 43 women). The demographic and clinical characteristics of the 2 patient groups are presented in Table 1.

Procedures

Emotion processing and neurocognitive tasks were administered by trained personnel in a quiet laboratory testing room on a PowerLaboratory® platform running on MacOS.[51] The order of procedures was counterbalanced (Latin square design). Participants were given standard instructions and practice trials with feedback to assure comprehension. Response time for each stimulus was recorded. The data were stored on an internal spreadsheet and uploaded to a relational database.

Neurocognitive Measures

The computerized battery development and application in schizophrenia was described.[52,53] The battery was

Table 1. Demographic and Clinical Characteristics of Patients With Schizophrenia With Flat Affect (FA) and Without Flat Affect (NFA)

	FA			NFA				
	N	Mean	Std	N	Mean	Std	*t*	*p*
Demographic								
Age	63	29.5	8.8	99	33.3	9.1	2.93	.004
Age at onset		20.9	4.7		22.9	6.7	2.14	.034
Duration		7.4	7.5		9.4	8.2	1.53	NS
Education		12.2	1.9		13.5	2.4	3.73	.001
Parental education		13.9	2.8		13.8	3.4	0.08	NS
Clinical								
SANS								
Affective flattening		3.2	0.4		1.1	1.0	−17.83	< .0001
Alogia		2.2	1.2		0.8	1.2	−8.46	< .0001
Avolition		2.7	1.2		1.3	1.4	−6.99	< .0001
Anhedonia		3.1	1.2		2.0	1.3	−5.63	< .0001
Attention		1.9	1.4		0.7	1.1	−6.24	< .0001
SAPS								
Hallucinations		2.2	1.5		1.6	1.6	−2.83	.005
Delusions		2.3	1.4		2.0	1.5	−1.72	NS
Bizarre behavior		0.9	1.3		0.4	0.9	−3.44	.001
Thought disorder		1.3	1.3		0.9	1.2	−2.12	.035
Medication								
No meds								
Dose	19	N/A	N/A	26	N/A	N/A	N/A	N/A
Typicals								
Current dose	4	327.5	151.7	15	421.1	346.8	0.51	NS
ADD in chlorpromazine equivalents		373.8	229.9		252.0	152.1	1.15	NS
Atypicals								
Current dose	37	14.9	6.4	52	11.4	6.7	2.4	.0158
ADD* in olanzapine equivalents		13.5	5.8		11.1	6.0	1.79	NS
Both								
Current typical dose	3	700.0	282.8	6	416.7	288.7	1.09	NS
ADD		510.0	14.1		229.3	352.1	1.71	NS
Current atypical dose		17.9	15.2		11.7	7.7	0.63	NS
ADD		21.1	9.1		11.5	7.6	1.31	NS

Note: ADD = Average Daily Dose; N/A = not applicable; NS = not significant; SANS = Scale for Assessment of Negative Symptoms[44]; SAPS = Scale for Assessment of Positive Symptoms.[45]

administered in a fixed order using clickable icons. Its total administration time was approximately 55 minutes, including brief rest periods between tests. The following domains were assessed:

Abstraction and mental flexibility (ABF). The Penn Conditional Exclusion Test (PCET)[54] is a measure of abstraction and concept formation. Subjects decide which of 4 objects does not belong with the other 3 based on 1 of 3 sorting principles. Sorting principles change, and feedback is used to develop new strategies (Time: 12 minutes).

Attention (ATT). The Penn Continuous Performance Test (PCPT)[52] uses a CPT paradigm. The participant responds to a set of 7-segment displays whenever they form a digit or letter (Time: 8 minutes).

Verbal Memory (VME). The Penn Word Memory Test[52] presents 20 target words that are then mixed with 20 distracters equated for frequency, length, concreteness, and low imageability. A 20 minute delayed recognition procedure is also administered (Time: 4 minutes).

Face Memory (FME). The Penn Face Memory Test[52] presents 20 digitized faces that are then mixed with 20 distracters equated for age, gender, and ethnicity. The recognition procedure is repeated after a 20-minute delay (Time: 4 minutes).

Spatial Memory (SME). The Visual Object Learning Test (VOLT)[55] uses Euclidean shapes as stimuli with the same paradigm as the word and face memory tasks (Time: 4 minutes).

Language (LAN). The Penn Verbal Reasoning Test[52] consists of verbal analogy problems from the ETS factor-referenced test kit (Time: 5 minutes).

Spatial Processing (SPA). Judgment of Line Orientation[56] presents 2 lines at an angle, and participants

indicate the corresponding lines on a simultaneously presented array (Time: 6 minutes).

Sensory-Motor Dexterity (SM).[52] The task requires the participant to move the mouse and click as quickly as possible on a green square that disappears after the click. The square gets increasingly small (Time: 2 minutes).

Emotion Processing Measures

Two computerized tasks were administered in a counterbalanced order.

The Penn Emotion Acuity Test (PEAT)[18,31] consists of 10 happy, 10 sad, and 20 neutral expressions of Caucasian faces. The task requires the participant to indicate the emotion depicted on a 7-point Likert-type intensity scale (1 = very sad, 2 = moderately sad, 3 = somewhat sad, 4 = neutral, 5 = somewhat happy, 6 = moderately happy, 7 = very happy).

The Emotion Intensity Differentiation task (Emodiff) presents 2 faces of the same individual showing the same emotion (happy or sad), requiring the participant to select the more intense expression. A total of 40 face pairs (20 happy, 20 sad) are used.[35]

Data Analysis

To establish whether flat affect is uniquely related to emotion processing performance, a stepwise regression analysis was conducted, predicting emotion processing performance efficiency from the negative symptoms scores. To examine the impact of flat affect on clinical and outcome variables, FA versus NFA served as a grouping factor in multivariate analyses of variance (MANOVAs) performed separately on the PAS, QOL, and LEV scores. The computerized emotion processing and neurocognitive measures were analyzed similarly. For each computerized test, accuracy (number of items correct) and speed (median response time in milliseconds for correct answers) were determined and transformed to standard equivalence units (z-scores) using normative data available at the SCR.[18,52] Efficiency of performance was defined as Accuracy/log(Speed) (items correct per unit time, the log transformation is recommended for response time data). The FA versus NFA contrast was a grouping factor in a group × sex × task mixed model, performed separately for the emotion processing and the neurocognitive tasks. Mixed model analysis was preferred over MANOVAs because not all subjects had all scores and to improve generalizability beyond the current sample. For the neurocognitive tasks we limited the examination to efficiency scores, and for the emotion processing tasks we examined accuracy and speed separately.

Results

The regression analysis supported the focus of the present study on flat affect. When efficiency of performance on the emotion processing tasks (averaged across both tasks) was entered as the dependent measure to be predicted from the SANS subscales, the affect scale entered first and was a highly significant predictor; $F = 11.98$, $df = 1,190$, $p = .0007$. No other SANS scale or any of the SAPS scales significantly improved the model.

Clinical

The hypothesis of an association between flat affect and clinical variables was supported. Patients with FA had poorer premorbid adjustment (PAS, Figure 1, left panel), relative to NFA patients (n = 28 and 52, respectively, as these include only patients on whom these data were rated as reliable); $F = 14.33$, $df = 1,78$, $p = .0003$. Quality of life (QOL, Figure 1, middle panel) was also substantially lower for FA patients compared with NFA patients; $F = 36.37$, $df = 1,160$, $p < .0001$, and FA patients scored more poorly on functional outcome measures (LEV, Figure 1, right panel) at 1-year follow-up; $F = 17.62$, $df = 1,160$, $p < .0001$. Entering education, parental education, and age as covariates did not affect the significance of the findings appreciably.

Emotion Processing

Comparing patients and controls. A diagnosis × accuracy versus speed × PEAT versus Emodiff × happy versus sad mixed model analysis showed a significant main effect of diagnosis, $F = 66.58$, $df = 1,290$, $p < .0001$, patients, relative to controls, performed less accurately and more slowly; task, $F = 5.10$, $df = 1,170$, $p = .0252$, poorer performance for the Emodiff than PEAT across groups; diagnosis × accuracy versus speed, $F = 6.15$, $df = 1,286$, $p = .0137$, patients were more impaired in accuracy than in speed; and a highly significant 4-way interaction of diagnosis × accuracy versus speed × PEAT versus Emodiff × happy versus sad, $F = 9.55$, $df = 8,744$, $p < .0001$. Decomposition of this interaction showed that while patients were impaired for accuracy across tasks, $F = 82.03$, $df = 1,290$, $p < .0001$, they were less accurate on the Emodiff than the PEAT, $F = 8.90$, $df = 1,170$, $p = .0033$. For speed, while the overall diagnosis effect was significant, reflecting slower response times in patients, $F = 18.32$, $df = 1,290$, $p < .0001$, it was overshadowed by a diagnosis × test interaction, $F = 25.53$, $df = 1,170$, $p < .0001$. Patients performed both less accurately and faster than controls on the Emodiff. Entering education, parental education, and age as covariates did not affect the significance of the findings appreciably.

Contrasting the FA and NFA groups. Patients with FA performed less accurately than NFA patients across PEAT and Emodiff, $F = 4.26$, $df = 1,191$, $p = .0403$, but they did not differ in speed, $F < 1$. A highly significant interaction of group × accuracy versus speed × PEAT versus Emodiff × happy versus sad, $F = 7.95$,

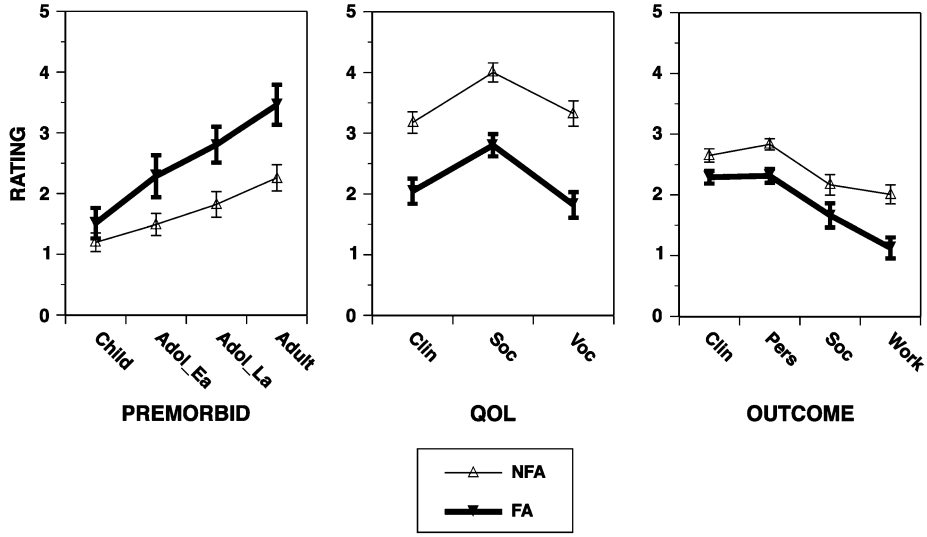

Fig. 1. Level of Function Ratings (mean ± SEM) in Patients With Flat Affect (FA) and No Flat Affect (NFA). Premorbid Adjustment Scale (PAS, left panel) in childhood (Child), early adolescence (Adol-Ea), late adolescence (Adol-La), and adulthood (Adult). Higher scores indicate poorer functioning. Quality of Life (QOL, middle panel) for clinical (Clin), social (Soc), and vocational (Voc) domains. Higher values indicate better functioning. Outcome (LEV, right panel) for clinical (Clin), personal (Pers), social (Soc), and work domains. Higher values indicate better functioning.

df = 8,511, $p < .0001$, indicated that patients with FA were both less accurate and slower than NFA patients for the PEAT, while they were less accurate but faster for the Emodiff. When sex was added as a grouping factor, a significant sex × affect group × accuracy versus speed × PEAT versus Emodiff × happy versus sad was evident, $F = 4.96$, *df* = 16,736, $p < .0001$, indicating that the effect of grouping by flat affect was more pronounced for men. Specifically, men with flat affect seem more impaired for both speed and accuracy on the PEAT compared with men without flat affect (Figure 2). Entering education, parental education, and age as covariates did not affect the significance of the findings appreciably.

Neurocognitive Measures

The impaired performance of patients with FA on emotion processing tasks does not seem to be part of a more generalized cognitive deficit. The mixed model analysis

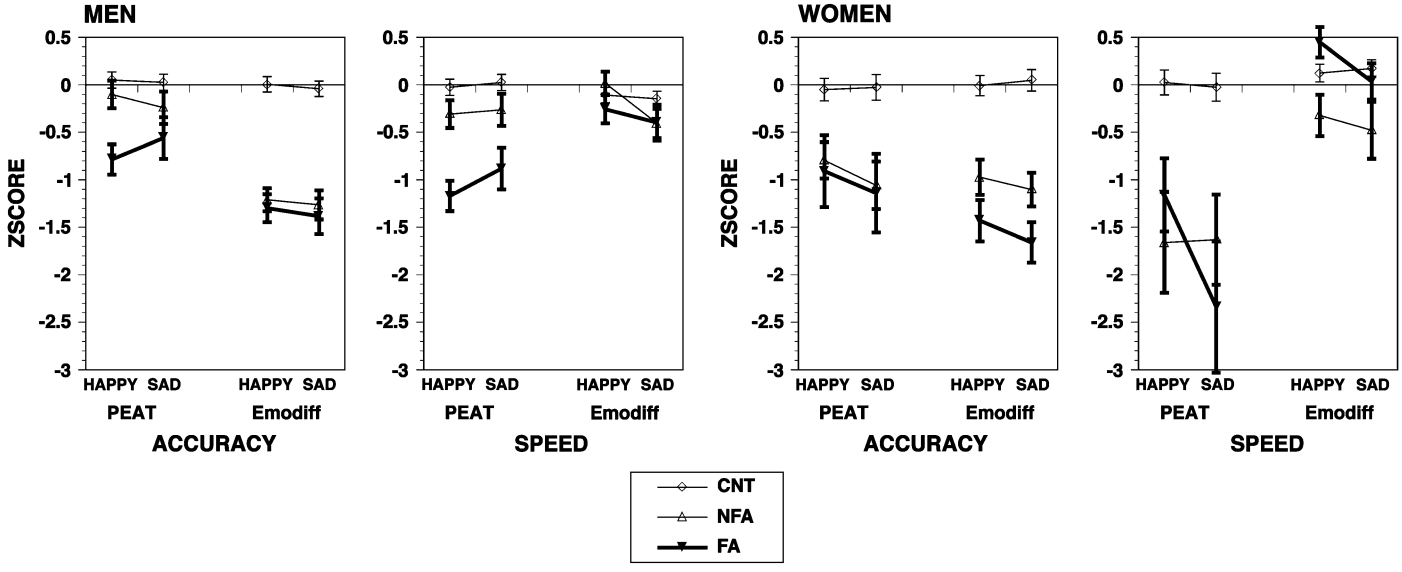

Fig. 2. PEAT and Emodiff Performance (*z*-score mean+SEM for accuracy and speed) in FA and NFA Patients and Controls (CNT) by Sex. The *z*-scores for speed were reversed to reflect poorer performance by lower scores.

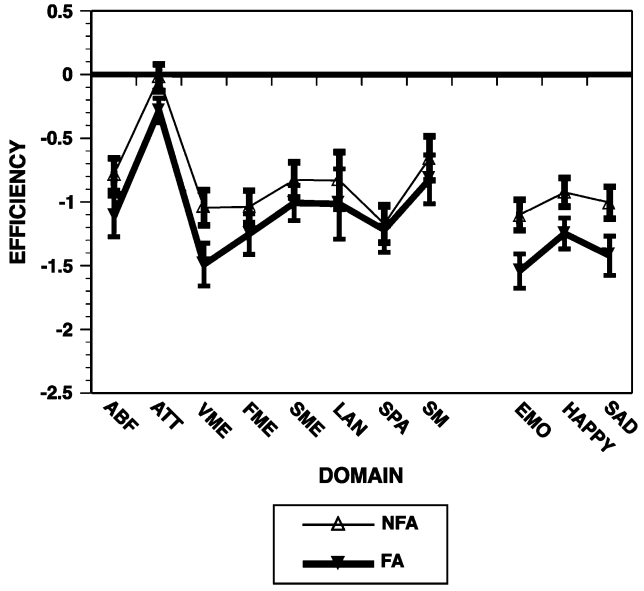

Fig. 3. Neurocognitive and Emotion Processing Performance (*z*-score mean ± SEM for efficiency) in FA and NFA Groups. ABF = Abstraction/flexibility; ATT = Attention; VME = Verbal Memory; SME = Spatial Memory; FME = Facial Memory; LAN = Language; SPA = Spatial; SM = Sensor-motor; Emo = Average emotion processing tests.

contrasting the average efficiency on the emotion processing tasks (*z*-scores averaged across PEAT and Emodiff) with the neurocognitive domains showed a significant group (FA versus NFA) × emotion-cognition interaction, $F = 42.40$, $df = 3,182$, $p < .0001$. As can be seen in Figure 3, performance on the emotion processing tasks was impaired for patients with FA relative to NFA patients (right side of Figure 3), while the profile of the subgroups on the computerized neurocognitive battery overlaps. There was a significant group × domain interaction within the cognitive domains, $F = 8.33$, $df = 13, 865$, $p < .0001$, but the only function where patients with FA performed significantly worse was verbal memory. Entering education, parental education, and age as covariates did not affect the significance of the findings appreciably.

It is noteworthy that performance on the emotion processing tasks was correlated with performance on the neurocognitive measures. These correlations were all significant (at $p < .0001$) but moderate: ABF = 0.44; ATT = 0.31; VME = 0.48; FME = 0.45; SME = 0.35; LAN = 0.40; SPA = 0.37.

Discussion

Our sample of patients with schizophrenia, dichotomized by the presence of clinically significant flat affect, showed that blunted affect is more common in men and is associated with distinct clinical features and deficits. The hypothesis that flat affect has an adverse effect on course of illness was strongly supported. Patients with FA had poorer premorbid adjustment, worse current quality of life, and worse outcome 1 year after affect was assessed. The poorer clinical picture begins with early adolescence and seems to span all facets of social adjustment. Notably, patients with FA also had more severe negative symptoms on other domains including avolition, alogia, anhedonia, and attention, while the positive symptoms in this group were slightly more severe. Although the focus of this prospective study was on flat affect, other domains that define negative symptoms, and their interrelation merit further examination (see the other articles in this issue).

Demographic characteristics of the 2 groups do not seem to explain why patients with FA have poorer clinical course and outcome. The groups did not differ in parental education and hence came from a similar sociodemographic background. Patients with FA attained a lower educational level, but that could be related to their younger age and earlier age at onset. The groups did not differ in duration of illness. Indeed, flat affect was evident in patients early in the course of illness. Notably, the results were sustained after controlling for these factors. Similarly, the results did not differ for inpatients and outpatients or by medication status, consistent with previous findings from our group that treatment with typical or atypical medications does not influence functional outcome.[57] It is also noteworthy that the groups did not differ in dose or duration of treatment, except that patients with FA who were on atypicals only had a higher current dose than their counterparts without flat affect. While antipsychotics, in particular typicals, have been associated with akinesia, including the face, studies that have examined patients on and off antipsychotics reported no clear effect on expressivity and emotional experience.[58,59]

A major focus of the present study was to examine whether flat affect is associated with impaired emotion identification. As expected, patients with schizophrenia, compared with controls, were impaired on facial emotion processing tasks, one that required identification of happy and sad emotions and another that required differentiating among intensities within these emotions. Patients also showed the expectedly greater difficulties on the latter. Indeed, they displayed a "speed-accuracy decomposition,"[37,38] whereby they responded inaccurately but fast, signifying "surrender." These results suggest that future studies examining emotion processing deficits in schizophrenia should either use an emotion identification task or make intensity discrimination easier.

The main hypothesis of greater impairment in emotion processing for patients with FA was supported. Patients with FA performed more poorly on both tasks and showed a stronger decomposition of speed and accuracy for the intensity discrimination. Indeed, patients with FA

responded even faster than controls. While performance on emotion processing tasks correlated moderately with neurocognitive performance across domains, the two groups did not differ in the neurocognitive profile except for verbal memory. Thus, the more impaired performance in emotion processing in patients with FA cannot be attributed to a greater generalized cognitive deficit. These results differ from an earlier study by our group using traditional paper-and-pencil neuropsychological measures.[18] In that study we did not find differential deficit for emotion compared with an age identification task, but performance on the emotion task correlated with symptom severity and with measures of attention, verbal and spatial memory, and language. The present study has a much larger sample and shows moderate yet robust correlations between emotion processing and all neurocognitive measures. Furthermore, it shows unique associations for accuracy and speed that are not feasible with the traditional battery.

The link between cognition and emotion has been a topic of increased scrutiny.[39,40,60] It appears that the memory system, particularly that related to "episodic," "explicit," or "source" memory,[61,62] is closely associated with primary systems regulating emotion.[40] Our results showed specific deficit in verbal memory associated with flat affect. It is unclear why only verbal memory distinguished the groups, and a replication is warranted. Possibly, given the association of verbal memory with left hemispheric function, this finding suggests greater left temporolimbic dysfunction in patients with flat affect. Functional imaging could help identify brain systems involved in emotion processing and their interaction with those regions recruited for processing of non-emotional stimuli.[63]

This study has several limitations. The emotion processing stimuli included only happy and sad faces. Processing of other "universal emotions" such as anger and fear may show a different or a more specific relation to clinical features. We have developed tasks that examine other emotions[64] and have applied them to patients with schizophrenia.[33] Another limitation of the study is its reliance on clinical ratings of flat affect. While these ratings are obtained under structured conditions and are highly reliable, a better understanding of deficits in the expression of emotions could be obtained from quantitative automated measures of facial affect change.[65] Finally, the data on premorbid functioning is retrospective.[22] Therefore, caution should be used in the interpretation of results. For example, our data suggest that FA patients are indistinguishable from NFA patients in their adjustment during childhood. Prospective studies of children at risk will help establish early signs of flat affect.[66]

Notwithstanding these limitations, the results of the present investigation give strong support to the hypothesis that patients with schizophrenia are impaired in emotion processing and that, among patients, those with flat affect are especially impaired. Furthermore, the association between flat affect and poor functioning underscores the need to examine this facet of the disorder. Other negative symptom domains, such as anhedonia, could likewise relate to emotion processing and outcome.[67,68] However, our focus on flat affect is supported by the regression analysis and could yield mechanistic models, especially considering the overlap between neural systems involved in emotion processing and those involved in memory. The possibility that flat affect in schizophrenia may be associated with a unique neural substrate is therefore furthered by the impairment in verbal memory in patients with flat affect, while other neurocognitive measures were similar to patients without flat affect.

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References

1. Bleuler E. *Dementia Praecox*. Zinkin J, trans. New York, NY: International Universities Press; 1950.
2. Kraepelin E. *Dementia Praecox*. Barclay RM, trans. Edinburgh: Scotland: Livingstone; 1919.
3. Carpenter WT Jr. Clinical constructs and therapeutic discovery. *Schizophr Res.* 2004;72:69–73.
4. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Cannon TD, Gur RC. Phenomenology and functioning in first episode schizophrenia. *Schizophr Bull.* 1992;18:449–462.
5. Goldstein JM, Seidman LJ, Goodman JM, et al. Are there sex differences in neuropsychological functions among patients with schizophrenia? *Am J Psychiatry.* 1998;155:1358–1364.
6. Gur RE, Petty RG, Turetsky BI, Gur RC. Schizophrenia throughout life: sex differences in severity and profile of symptoms. *Schizophr Res.* 1996;2:1–12.
7. Shtasel DL, Gur RE, Gallacher FV, Heimberg C, Gur RC. Gender differences in the clinical expression of schizophrenia. *Schizophr Res.* 1992;7:225–232.
8. Krause R, Steimer E, Sanger-Alt C, Wagner G. Facial expressions of schizophrenic patients and their interaction partners. *Psychiatry.* 1989;52:1–12.
9. Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. *J Abnorm Psychol.* 1992;101:37–44.
10. Kring AM, Kerr S, Smith DA, Neale JM. Flat affect in schizophrenia does not reflect diminished subjective experience of emotion. *J Abnorm Psychol.* 1993;104:507–517.
11. Dworkin RH. Affective deficits and social deficits in schizophrenia: what's what? *Schizophr Bull.* 1992;18:59–64.
12. Archer J, Hay DC, Young AW. Face processing in psychiatric conditions. *Br J Clin Psychol.* 1992;31:45–61.
13. Bediou B, Franck N, Saoud M, et al. Effects of emotion and identity on facial affect processing in schizophrenia. *Psychiatry Res.* 2005;133:149–157.
14. Cutting J. Judgment of emotional expression in schizophrenics. *Br J Psychiatry.* 1981;139:1–6.

15. Feinberg TE, Rifkin A, Schaffer C, Walker E. Facial discrimination and emotional recognition in schizophrenia and affective disorders. *Arch Gen Psychiatry.* 1986;43:276–279.
16. Heimberg C, Gur RE, Erwin RJ, Shtasel DL, Gur RC. Facial emotion discrimination: III. behavioral findings in schizophrenia. *Psychiatry Res.* 1992;42:253–265.
17. Kerr SL, Neale JM. Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? *J Abnorm Psychol.* 1993;102:312–318.
18. Kohler CG, Bilker W, Hagendoorn M, Gur RE, Gur RC. Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. *Biol Psychiatry.* 2000;48:127–136.
19. Mandal MK, Pandey R, Prasad AB. Facial expressions of emotions and schizophrenia: a review. *Schizophr Bull.* 1998;24:399–412.
20. Sachs G, Steger-Wuchse D, Kryspin-Exner I, Gur RC, Katschnig H. Facial recognition deficits and cognition in schizophrenia. *Schizophr Res.* 2004;68:27–35.
21. Shaw RJ, Dong M, Lim KO, Faustman WO, Pouget ER, Alpert M. The relationship between affect expression and affect recognition in schizophrenia. *Schizophr Res.* 1999;37:245–250.
22. Walker EF, McGuire M, Bettes B. Recognition and identification of facial stimuli by schizophrenics and patients with affective disorders. *Br J Clin Psychol.* 1984;23: 37–44.
23. Kring AM, Neale JM. Do schizophrenia patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? *J Abnorm Psychol.* 1996;105:249–257.
24. Aghevli MA, Blanchard JJ, Horan WP. The expression and experience of emotion in schizophrenia: a study of social interactions. *Psychiatry Res.* 2003;119:261–270.
25. Kohler CG, Gur RC, Gur RE. Emotional processes in schizophrenia: a focus on affective states. In: Borod JC, ed. *The Neuropsychology of Emotion.* New York, NY: Oxford University Press; 2000.
26. Sweet LH, Primeau M, Fichtner CG, Lutz G. Dissociation of affect recognition and mood state from blunting in patients with schizophrenia. *Psychiatry Res.* 1998;81:301–308.
27. Lewis SF, Garver DL. Treatment and diagnostic subtype in facial affect recognition in schizophrenia. *Psychiatry Res.* 1995;29:5–11.
28. Cramer P, Weegmann M, O'Neil M. Schizophrenia and the perception of emotions: how accurately do schizophrenics judge the emotional states of others? *Br J Psychiatry.* 1989;155:225–228.
29. Blanchard JJ, Kring M, Neale JM. Flat affect in schizophrenia: a test of neuropsychological models. *Schizophr Bull.* 1994;20:311–325.
30. Blanchard JJ, Neale JM. The neuropsychological signature of schizophrenia: generalized or differential deficit? *Am J Psychiatry.* 1994;151:40–48.
31. Erwin RJ, Gur RC, Gur RE, Skolnick BE, Mawhinney-Hee M, Smailis J. Facial emotion discrimination: I. task construction and behavioral findings in normals. *Psychiatry Res.* 1992;42:231–240.
32. Schneider F, Gur RC, Gur RE, Muenz L. Standardized mood induction with happy and sad facial expressions. *Psychiatry Res.* 1994;51:19–31.
33. Kohler CG, Turner TH, Bilker WB, et al. Facial emotion recognition in schizophrenia: intensity effects and error pattern. *Am J Psychiatry.* 2003;160:1768–1774.
34. Kohler CG, Turner TH, Stolar NM, et al. Differences in facial expressions of four universal emotions. *Psychiatry Res.* 2004;128:235–244.
35. Silver H, Shlomo N, Turner T, Gur RC. Perception of happy and sad facial expressions in chronic schizophrenia: evidence for two evaluative systems. *Schizophr Res.* 2002;55:171–177.
36. Schneider F, Gur RC, Gur RE, Shtasel DL. Neurobehavioral probes in relation to psychopathology. *Schizophr Res.* 1995;17:67–75.
37. Meyer DE, Irwin DE, Osman AM, Kounios J. The dynamics of cognition and action: mental processes inferred from speed-accuracy decomposition. *Psychol Rev.* 1988;95:183–237.
38. Smith RW, Kounios J. Sudden insight: all-or-none processing revealed by speed-accuracy decomposition. *J Exp Psychol Learn Mem Cogn.* 1996;22:1443–1462.
39. Damasio AR. Emotion in the perspective of an integrated nervous system. *Brain Res Rev.* 1998;26:83–86.
40. Rolls ET. Memory systems in the brain. *Annu Rev Psychol.* 2000;51:599–630.
41. Gur RE, Mozley PD, Resnick SM, et al. Relations among clinical scales in schizophrenia: overlap and subtypes. *Am J Psychiatry.* 1991;148:472–478.
42. First M, Spitzer R, Williams J, Gibbon M. *Structured Clinical Interview for DSM-IV: Patient Version (SCID-P).* New York, NY: New York State Psychiatric Institute, Biometrics Research Department; 1996.
43. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV.* 4th ed. Washington, DC: American Psychiatric Press; 1994.
44. Andreasen NC. *The Scale for the Assessment of Negative Symptoms (SANS).* Iowa City, Iowa: University of Iowa; 1984.
45. Andreasen NC. *The Scale for the Assessment of Positive Symptoms (SAPS).* Iowa City, Iowa: University of Iowa; 1984.
46. Cannon-Spoor H, Potkin S, Wyatt R. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull.* 1982;8:470–484.
47. Heinrichs D, Hanlon T, Carpenter WJ. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull.* 1984;10:388–398.
48. Strauss JS, Carpenter WT Jr. The prediction of outcome in schizophrenia: I. characteristics of outcome. *Arch Gen Psychiatry.* 1972;27:739–746.
49. Shtasel DL, Gur RE, Mozley PD, et al. Volunteers for biomedical research: recruitment and screening of normal controls. *Arch Gen Psychiatry.* 1991;48:1022–1025.
50. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition (SCID-NP).* New York, NY: New York State Psychiatric Institute, Biometrics Research Department; 1995.
51. Chute DL, Westall RF. *PowerLaboratory* Devon, Pa: MacLaboratory, Incorporated; 1997.
52. Gur RC, Ragland JD, Moberg PJ, et al. Computerized neurocognitive scanning: I. methodology and validation in healthy people. *Neuropsychopharmacology.* 2001;25:766–776.
53. Gur RC, Ragland JD, Moberg PJ, et al. Computerized neurocognitive scanning: II. the profile of schizophrenia. *Neuropsychopharmacology.* 2001;25:777–788.
54. Kurtz MM, Ragland JD, Moberg PJ, Gur RC. The Penn Conditional Exclusion Test: a new measure of executive-function with alternate forms of repeat administration. *Arch Clin Neuropsychol.* 2004;19:191–201.

55. Glahn DC, Gur RC, Ragland JD, Censits DM, Gur RE. Reliability, performance characteristics, construct validity, and an initial clinical application of a Visual Object Learning Test (VOLT). *Neuropsychology.* 1997;11:602–612.
56. Benton AL, Varney NR, Hamsher K. *Judgment of Line Orientation, Form V.* Iowa City, Iowa: University of Iowa Hospitals; 1975.
57. Siegel SJ, Irani F, Brensinger CM, et al. Prognostic variables at intake and long-term level of function in schizophrenia. *Am J Psychiatry.* 2006;163:1–9.
58. Earnst KS, Kring AM, Kadar MA, Salem JE, Shepard DA, Loosen PT. Facial expression in schizophrenia. *Biol Psychiatry.* 1996;40:556–558.
59. Kring AM, Kerr SL, Earnst KS. Schizophrenic patients show facial reactions to emotional facial expression. *Psychophysiology.* 1999;36:186–192.
60. Lang PJ. The varieties of emotional experience: a meditation on James-Lange theory. *Psychol Rev.* 1994;101: 211–221.
61. Reber PJ, Squire LR. Encapsulation of implicit and explicit memory in sequence learning. *J Cogn Neurosci.* 1998;10:248–263.
62. Schacter DL, Norman KA, Koustaal W. The cognitive neuroscience of constructive memory. *Annu Rev Psychol.* 1998;49:289–318.
63. Gur RE, McGrath C, Chan RM, et al. An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry.* 2002;159:1992–1999.
64. Gur RC, Sara R, Hagendoorn M, et al. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *J Neurosci Methods.* 2002;115:137–143.
65. Verma R, Davatzikos C, Loughead J, et al. Quantification of facial expressions using high-dimensional shape transformations. *J Neurosci Methods.* 2005;141:61–73.
66. Walker EF, Grimes KE, Davis DM, Smith AJ. Childhood precursors of schizophrenia: facial expressions of emotion. *Am J Psychiatry.* 1993;150:1654–1660.
67. Mueser KT, Doonan R, Penn DL, et al. Emotion recognition and social competence in chronic schizophrenia. *J Abnorm Psychol.* 1996;105:271–275.
68. Kee KS, Green MF, Mintz J, Brekke JS. Is emotion processing a predictor of functional outcome in schizophrenia? *Schizophr Bull.* 2003;29:487–497.