

Startle Gating Deficits in a Large Cohort of Patients With Schizophrenia

Relationship to Medications, Symptoms, Neurocognition, and Level of Function

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Context: Patients with schizophrenia exhibit deficits in automatic, preattentive sensorimotor gating (prepulse inhibition [PPI]) of the startle reflex.

Objective: To assess the relationships between PPI deficits and demographic, clinical, neurocognitive, and functional status in a large cohort of patients with schizophrenia.

Design: Cross-sectional comparison of patients with schizophrenia and normal comparison subjects.

Setting: University-based psychophysiology laboratory.

Participants: Carefully screened patients with schizophrenia (n=103) and normal comparison subjects (n=66).

Main Outcome Measures: Participants were assessed in structured clinical interviews and tested in measures of acoustic startle PPI and neurocognition. The level of functioning was assessed in patients using validated scales. Analyses first compared all of the patients vs normal comparison subjects. Patients were then divided based on sex, medications, smoking status, and levels of PPI. The associations of PPI to clinical, neurocognitive, and

functional variables were assessed using both continuous and categorical analyses.

Results: Compared with normal comparison subjects, patients exhibited PPI deficits at 60-millisecond intervals but not at 30- or 120-millisecond intervals. In addition, patients exhibited deficits in neurocognition. Among patients, PPI levels were associated with sex (higher in men than in women), medication status (highest in patients treated with atypical antipsychotics), and smoking (higher in smokers than in nonsmokers). Compared with patients in the highest quartile of PPI, those in the lowest quartile of PPI were significantly more impaired on specific functional measures but did not differ in neurocognitive measures or symptom severity. The relationship between low PPI and functional impairment was most pronounced and orderly in male patients.

Conclusions: These findings highlight several important factors (sex, medications, and smoking status) that strongly impact the study and interpretation of PPI deficits in patient populations. These results also support the concept that deficient PPI is associated with impaired functional status in schizophrenia.

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CORE FEATURES OF SCHIZOPHRENIA include cognitive and emotional disturbances that may be linked to a disruption in the normal processing and/or hierarchical organization of sensory and cognitive information.^{1,2} Furthermore, disturbances in perception, thought and language structure, and behavioral organization in schizophrenia may result from impaired automatic, preconscious inhibitory mechanisms that normally regulate the quantity and quality of sensory and cognitive information that reaches consciousness.²⁻⁶ The loss of information-protective mechanisms in schizophrenia is a feature of models span-

ning psychological and neurobiological domains.^{1,3,7,8} Laboratory measures of deficient inhibition are used to understand the neural and molecular mechanisms of schizophrenia⁹⁻¹¹ as biomarkers for drug development¹² and as endophenotypes to identify schizophrenia genes.¹³

Patients with schizophrenia are deficient in 1 form of automatic, preconscious inhibition: sensorimotor gating as assessed by prepulse inhibition (PPI) of startle.^{5,14-30} Prepulse inhibition is the automatic suppression of startle magnitude that occurs when the startling stimulus is preceded 30 to 500 milliseconds by a weak prepulse.³¹⁻³³ Reduced PPI in schizophrenia is detected under specific experimen-

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Table 1. Participant Characteristics

Characteristic	NCSs	Patients With Schizophrenia
Age, mean (range), y*	33.54 (18-62)	43.98 (20-65)
Male/female, No.*	28/38	72/31
Women in follicular/luteal menstrual phase, No.†	16/19	8/4
Education, mean (range), y*	15.12 (7-20)	12.28 (6-22)
Marital status, No.		
Married	11	8
Engaged	2	1
Divorced	3	21
Separated	0	4
Widowed	1	3
None of the above	48	66
Handedness, right/left/ambidextrous, No.	60/6/0	88/12/2
Smoking, mean, No. of packs/d*	0.03	0.63
Participants excluded from study, No.		
Startle <10 units, No. (%)	14 (17)	30 (20)
Hearing threshold >40 dB on A scale	0	2
Positive urine toxicological results	1	3
Medical or psychiatric condition‡	6	10
Family history of schizophrenia	2	0
Other	3	2

Abbreviation: NCS, normal comparison subject.

* $P < .001$ for NCSs vs patients.

†Follicular indicates days 1 through 14 of the menstrual cycle; luteal indicates days 15 through 28 of the menstrual cycle. Self-reported dates were obtained from 35 NCSs and 12 patients.

‡Examples of medical or psychiatric conditions include history of electroconvulsive therapy, current substance abuse, and inappropriate diagnosis (schizoaffective disorder).

tal conditions and is among the most consistent and robust markers of brain-based inhibitory deficits in this disorder.

Less consistent is the evidence that this deficit in preattentive sensorimotor inhibition contributes to symptomatic, cognitive, or functional impairment in schizophrenia. Studies^{18,34,35} report weak or no significant correlations between PPI and symptom severity in schizophrenia. Some evidence links deficient PPI to the core schizophrenia trait, rather than symptoms, or cognitive and functional impairment.^{25,36-39} Others^{19,22,23,26,29} report deficient PPI only in symptomatic patients that partially or completely resolves with medication treatment.

Several factors might account for conflicting evidence linking PPI to clinical, cognitive, and functional deficits in schizophrenia. First, perhaps no such relationships exist; PPI deficits in schizophrenia might reflect brain processes that do not contribute to these other domains. Second, conflicting findings may reflect the fact that patient cohorts across studies range from outpatient to inpatient to mixed samples whereas control cohorts range from hospital or university employees to broader community samples. Third, conflicting findings may reflect different experimental designs; PPI is highly sensitive to stimulus parameters, including prepulse characteristics that differ substantially across published studies^{35,40} in patients with schizophrenia. Fourth,

most studies are adequately powered to detect group differences in patients vs normal comparison subjects (NCSs) but not to detect symptom correlates of PPI in patients. This problem is exacerbated by “ceiling-level” symptoms and “floor-level” functioning in patients, resulting in restricted ranges that complicate correlational strategies. Furthermore, patient cohorts differ in terms of factors that influence PPI, including sex distribution and menstrual phase,^{34,41-44} medication status,²⁰ and smoking history.⁴⁵ These influences, together with the heterogeneity of neural dysfunction in schizophrenia, add variance that—without large cohorts—might obscure the detection of clinical or symptom correlates of PPI.

In this study, PPI was measured in large cohorts of patients (n=103) and NCSs (n=66) to achieve the power necessary to definitively test the hypothesis that PPI deficits in patients with schizophrenia are significantly related to measures of symptom severity, neurocognitive performance, and functional impairment and are moderated by several specific variables, including sex, antipsychotic medications (APs), and smoking status.

METHODS

Patients with schizophrenia were referred by physicians and long-term care facilities and were carefully screened to rule out drug abuse or dependence and neurologic insults. After a detailed description of study participation, written consent was obtained (University of California, San Diego, institutional review board protocol number 040564). Diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition.⁴⁶ Normal comparison subjects answered advertisements and underwent comprehensive clinical interviews (via the Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-patient Edition)⁴⁷ and toxicological screens to rule out Axis I or II diagnoses or current recreational drug use. Audiometry (Saico Model SCR-2; Assens, Denmark) excluded subjects who could not detect 1-kHz 40-dB tones. Nonreactive subjects (mean startle magnitude <13.1 μ V [10 digital units] in the first trial block containing prepulse trials) were excluded as per the article by Braff et al.¹⁴ The recruitment target goal was 100 patients; the final sample included 103 patients and 66 NCSs.

Demographics and clinical characteristics of all of the participants are shown in **Table 1** and **Table 2**. Compared with the final NCS group, the final patient group was older and had greater representation of men and smokers. Limited information on menstrual dates was obtained from patients either based on the use of medications that prevented normal cycles⁴⁸ or because of grossly impaired self-reporting. Most patients were quite impaired, had longstanding illness, and were medicated with atypical APs. Symptoms were assessed with the Scale for the Assessment of Positive Symptoms (SAPS)⁴⁹ and the Scale for the Assessment of Negative Symptoms (SANS).⁵⁰ Neurocognitive measures⁵¹⁻⁵⁶ are listed in **Table 3**. Functional status was assessed with the Global Assessment of Functioning (GAF) scale,⁵⁷ the University of California, San Diego, Performance-based Skills Assessment (UPSA) scale,⁵⁸ the Scale of Functioning (SOF),⁵⁹ and the Level of Independent Living (LIL) scale.⁶⁰ The GAF scale⁵⁷ assesses overall function across psychological, social, and occupational domains. The UPSA scale⁵⁸ measures performance in situations considered necessary for independent functioning: (1) general organization and planning; (2) finance; (3) social situations or communications; (4) transportation; and (5) household chores. The SOF⁵⁹ assesses func-

Table 2. Characteristics of Patients With Schizophrenia

Characteristic	Value
Age at onset of psychotic symptoms, mean (range), y	23.57 (8-42)
Duration of illness, mean (range), y	20.42 (2-53)
Duration with no psychiatric hospitalizations, mean (range), y	8.74 (0-80)
Patients receiving medication type, No.	
No AP	9
Typical AP (exclusively)	9
Atypical AP (exclusively)	67
Typical + atypical APs	18
GAF scale score, mean (SD)	41.58 (9.40)
SOF score, mean (SD)	48.54 (7.08)
UPSA scale score, mean (SD)	81.47 (13.45)
Patients in living setting, No.	
Structured facility or board and care	39
Significant family support or lives with parents	19
Independent living	45
SANS score, mean (SD)	11.73 (4.51)
SAPS score, mean (SD)	8.52 (4.33)

Abbreviations: AP, antipsychotic medication; GAF, Global Assessment of Functioning; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SOF, Scale of Functioning; UPSA, University of California, San Diego, Performance-based Skills Assessment.

tion in 5 domains: (1) orientation; (2) appointment compliance; (3) financial management; (4) socialization; and (5) independence of living. The LIL scale (modified from articles by Rapaport et al⁵⁹ and Twamley et al⁶⁰) categorizes independence in living: (1) living in a structured or semistructured setting, eg, long-term treatment facility or board and care facility; (2) living with family or requiring regular help from family, friends, or social services; and (3) living independently in an apartment or house.

Subjects abstained from smoking for at least 20 minutes prior to testing. They sat in a recliner chair in a sound-attenuated room. Methods followed those in previous articles.^{18,21,30} Two 4-mm silver-silver chloride electrodes were positioned below and lateral to each eye over the orbicularis oculi (resistance < 10 Ω), with a ground electrode behind the left ear. Electromyographic activity was directed through an SR-LABORATORY monitoring system (San Diego Instruments, Inc, San Diego) that recorded 250-millisecond epochs starting with startle stimulus onset (1-kHz sampling rate); blink scoring parameters were described previously.¹⁴ Electromyographic activity was band-pass filtered (0.1-1.0 kHz). Startle stimuli were presented binaurally through headphones. The session included a total of 74 active and 18 no-stimulation trials, lasted 23.5 minutes, and began with a 5-minute acclimation to white noise at a 70-dB sound pressure level that continued throughout the session. Startle stimuli were 40-millisecond noise bursts at a 115-dB sound pressure level. Prepulses were 20-millisecond noise bursts 15 dB higher than background, with onset 30, 60, or 120 milliseconds prior to pulse onset. Five startle stimuli were presented at the beginning (block 1) and end (block 4) of the session to assess habituation. In blocks 2 and 3, pulse-alone (PA) trials and each of the 3 prepulse trial types were pseudorandomly intermixed (range of intertrial intervals, 11-19 seconds; mean intertrial interval, 15 seconds). In 18 no-stimulation trials, data were recorded without stimulus presentation to assess basal electromyographic activity (no significant main or interaction effects were noted).

Multivariate repeated-measures analyses of variance (ANOVAs) with Greenhouse-Geisser corrections and Fisher

Table 3. Neuropsychological Performance*

Test	Scores by NCSs, Mean (SEM)	Scores by Patients With Schizophrenia, Mean (SEM)	P Value
WRAT standard reading score†	108.17 (1.21)	89.76 (1.61)	<.001
LNS			
Forward‡	14.67 (0.35)	11.72 (0.31)	<.001
Reorder§	11.35 (0.34)	7.74 (0.29)	<.001
WCST-64			
Perseverative responses§	8.38 (0.72)	19.12 (1.70)	<.001
Categories completed	3.76 (0.17)	2.24 (0.22)	<.001
CVLT list A trials 1-5 (T score)§	56.68 (1.35)	37.95 (1.17)	<.001

Abbreviations: CVLT, California Verbal Learning Test; LNS, letter-number span; NCS, normal comparison subject; WRAT, Wide Range Achievement Test; WCST-64, Wisconsin Card Sorting Test-64 Card Version.

*Raw data from the neurocognitive measures can be found at <http://psychiatry.ucsd.edu/Swerdlow/>.

†Among patients, there is a significant correlation ($P < .02$) with the mean University of California, San Diego, Performance-based Skills Assessment scale score.

‡Among patients, there are significant correlations ($P < .02$) with the mean University of California, San Diego, Performance-based Skills Assessment scale, Scale of Functioning, and Global Assessment of Functioning scale scores.

§Among patients, there are significant correlations ($P < .02$) with the mean University of California, San Diego, Performance-based Skills Assessment scale, Scale of Functioning, and Global Assessment of Functioning scale scores and a significant difference ($P < .05$) in Level of Independent Living scale scores by the χ^2 test, low vs high quartile.

||Among patients, there are significant correlations ($P < .02$) with the mean University of California, San Diego, Performance-based Skills Assessment and Global Assessment of Functioning scale scores and a significant difference ($P < .05$) in Level of Independent Living scale scores by the χ^2 test, low vs high quartile.

protected least-significant difference post hoc comparisons were performed with diagnosis as a between-subject factor. For PPI percentage, $100 \times (1 - [\text{prepulse} + \text{pulse amplitude}] / [\text{pulse amplitude}])$, within-subject factors were block and prepulse interval. Because no main or interaction effects of block or eye side were observed in analyses of PPI or reflex latency, data were collapsed across blocks and eye side. The relationships between PPI and clinical, neurocognitive, and functional variables were assessed using the 60-millisecond prepulse interval (where PPI deficits were detected) via continuous (regression) and categorical (median or quartile split) strategies. To examine key relationships independent from moderating effects of sex, medication, and smoking status on PPI, separate analyses were conducted on men and women, on subjects not receiving atypical APs, and on non-smokers. Where inspection of the data revealed extreme values, analyses were confirmed using both nonparametric (eg, Spearman rank correlation, Mann-Whitney *U* test) and parametric (simple regression, ANOVA) analyses. In all cases, $\alpha = .05$. Where appropriate, effect sizes (*d*) are reported.⁶¹

RESULTS

OMNIBUS ANALYSES

Results of startle and PPI measures are seen in **Figure 1**. Analyses of variance of startle magnitude, habituation, and basal electromyographic activity revealed no significant differences across diagnosis or sex. For startle mag-

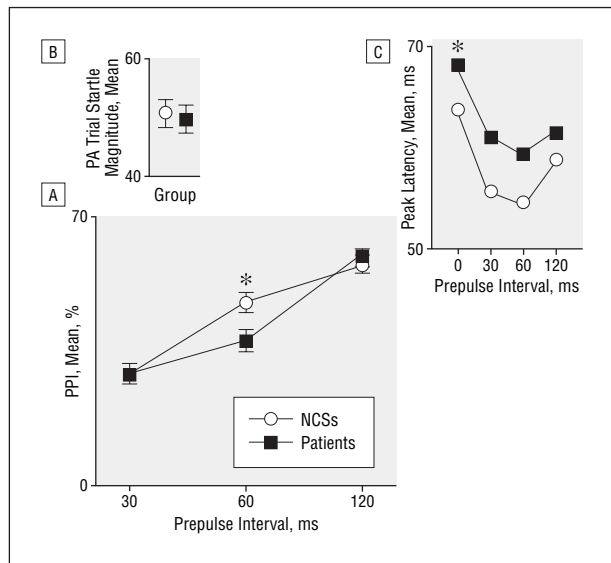


Figure 1. Startle measures in 103 patients with schizophrenia and 66 normal comparison subjects (NCSs). A, Mean prepulse inhibition (PPI) percentage for 30-, 60-, and 120-millisecond prepulse intervals in patients and NCSs. Error bars indicate SEM. *Significantly less PPI in patients as compared with NCSs for 60-millisecond prepulse intervals ($P < .04$) after significant interaction of diagnosis \times interval ($F_{2,330} = 4.42$, $P < .02$). B, Mean startle magnitude on pulse-alone (PA) trials. Analysis of variance of startle magnitude on PA trials revealed no effect of diagnosis ($F < 1$) or sex ($F_{1,165} = 1.72$, $P > .05$). Based on the potential sensitivity of PPI percentage to small differences in PA startle magnitude, analyses of PPI percentage were confirmed in groups in which PA startle magnitude was balanced precisely by eliminating the extreme deciles of PA values. Error bars indicate SEM. C, Mean peak reflex latency on PA trials (0-millisecond prepulse interval) and on trials with 30-, 60-, and 120-millisecond prepulse intervals. *Significantly slower reflex latency in patients than in NCSs ($F_{1,143} = 17.89$, $P < .001$) but no significant diagnosis \times trial type interaction ($F_{3,429} = 1.31$, $P > .05$). In some cases, SEM bars are too small to be discernable. While not part of the a priori hypotheses of this study, reflex latency on PA trials was found to be significantly greater among patients than among NCSs and correlated with age in patients ($R = 0.43$, $P < .001$) but not NCSs ($R = 0.14$) ($z = 1.98$; $P < .05$). Among patients, latency was unrelated to medication or smoking status and did not correlate significantly with neurocognitive or functional measures. Reflex latency was inversely related to Scale for the Assessment of Positive Symptoms scores ($R = -0.31$, $P < .002$) but not Scale for the Assessment of Negative Symptoms scores ($R = 0.04$); this relationship was evident among all Scale for the Assessment of Positive Symptoms subscales and was independent of age effects on latency.

nitude on PA trials, the diagnosis \times sex interaction approached significance ($P < .07$), reflecting a higher startle magnitude in men with schizophrenia than in male NCSs (mean [SEM] startle magnitude, 51.17 [2.89] vs 37.84 [2.99], respectively) and a higher startle magnitude in female NCSs than in women with schizophrenia (mean [SEM] startle magnitude, 60.09 [3.61] vs 47.13 [4.01], respectively). Among NCSs, no startle variables correlated significantly with age ($-0.23 < \text{all } r < 0.14$).

As expected, ANOVA of PPI revealed significant effects of sex (PPI in men $>$ PPI in women) and prepulse interval (PPI with 120-millisecond prepulse interval $>$ PPI with 60-millisecond prepulse interval $>$ PPI with 30-millisecond prepulse interval) as well as significant interactions of diagnosis \times interval and diagnosis \times sex \times interval. There was no significant main effect of diagnosis and no other informative 2-, 3-, or 4-way interactions. Post hoc comparisons at each prepulse interval revealed significantly greater PPI in NCSs than in patients only for 60-millisecond prepulse intervals ($P < .04$; $d = 0.24$) (Figure 1A).

Based on a near-significant diagnosis \times sex interaction for startle magnitude, we compared PPI in subgroups that were closely balanced for startle magnitude by eliminating the extreme decile (10%) of startle magnitude values from male and female NCSs and patients. These comparisons confirmed all of the significant main and interaction effects described earlier, including significantly reduced PPI in patients with schizophrenia as compared with NCSs for 60-millisecond prepulse intervals ($P < .04$).

MEDICATION

Patients were first classified as the following: not receiving medication ($n = 9$); receiving typical APs ($n = 9$); receiving atypical APs ($n = 67$); and receiving both typical and atypical APs ($n = 18$) (Table 2). Analysis of variance of PPI revealed a significant effect of medication status ($P < .001$), reflecting increased PPI among patients receiving atypical APs, and particularly among those receiving atypical APs, compared with patients not receiving medication (Figure 2A). Analyses of variance detected no significant effects of medication on startle magnitude or habituation or on clinical or functional measures (all $F < 1$).

Based on present and published^{19,20} evidence that atypical APs normalize PPI in schizophrenia and that PPI deficits persist (although perhaps in an attenuated form) among patients receiving only typical APs,^{5,14-24} a case-control matching strategy was used to analyze PPI in the 18 patients not receiving atypical APs. Each patient was matched to an NCS based on sex and age; if 2 NCSs met these characteristics, both were included in the analysis. This comparison revealed PPI deficits in patients that were robust and independent of prepulse interval or sex. Analysis of variance of PPI revealed significant effects of diagnosis (PPI in NCSs $>$ PPI in patients; $P < .02$) and prepulse interval, but there were no 2- or 3-way interactions.

Differences in PPI are most easily attributed to different levels of sensorimotor gating when groups differ in the sensitivity of startle to inhibition by prepulses but do not differ in startle to PA stimuli. In this case-matched sample, it was easy to precisely balance groups for mean startle magnitude on PA trials (Figure 2B). Analysis of variance of startle magnitude across all trial types revealed a significant interaction of diagnosis \times trial type, reflecting higher startle magnitude on prepulse trials in patients than in NCSs despite identical mean startle magnitude in patients and NCSs on PA trials. This provides definitive evidence for reduced sensorimotor gating in patients with schizophrenia; compared with their effects in NCSs, prepulses were significantly less effective in reducing the startle reflex in patients.

SMOKING

Studies^{45,62-65} have described PPI-enhancing effects of nicotine. Analysis of variance of PPI limited to non-smokers revealed significant effects of diagnosis (PPI in NCSs $>$ PPI in patients) (Figure 3), sex (PPI in men $>$ PPI in women), and interval as well as significant interactions of diagnosis \times sex, diagnosis \times interval, and

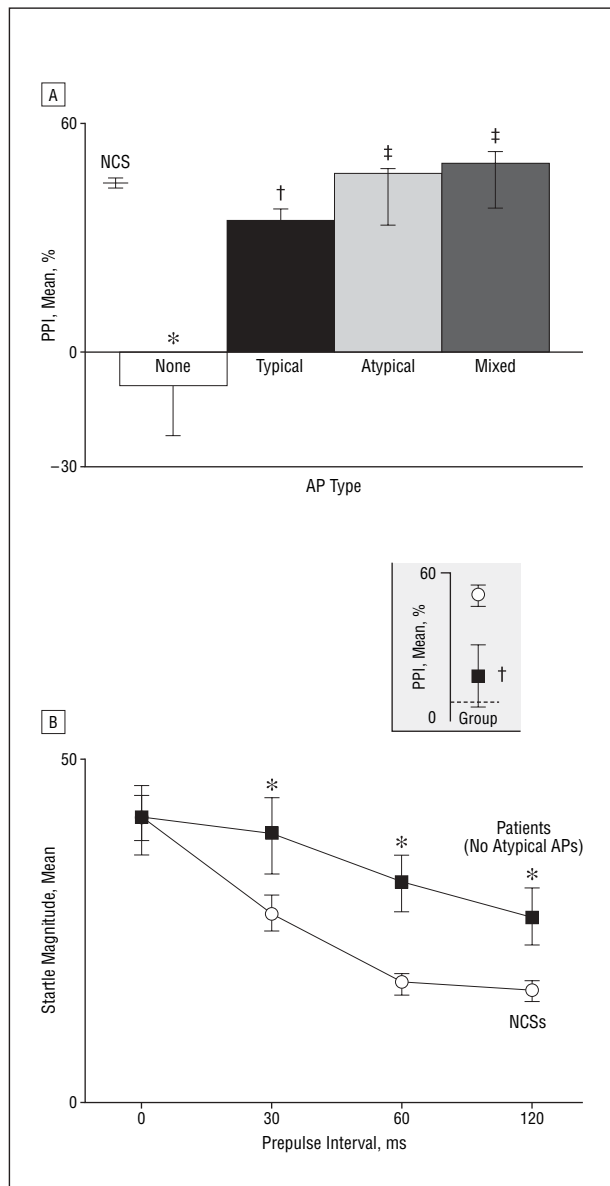


Figure 2. Medication effects on prepulse inhibition (PPI) in patients. A, Mean PPI percentage collapsed across prepulse intervals in patients treated with no antipsychotic medication (AP), typical APs, atypical APs, or both typical and atypical APs. Mean PPI percentage for normal comparison subjects (NCSs) is shown as a single point. Analysis of variance of PPI percentage in patients revealed a significant main effect of medication subgroups ($F_{3,95}=7.52, P<.001$), which was also significant when limited to 60-millisecond prepulse intervals ($F_{3,95}=6.06, P<.001$). Compared with PPI among NCSs, PPI was significantly reduced among unmedicated patients ($*P<.001$ by Fisher protected least-significant difference) and among all patients not receiving an atypical AP ($P=.001$); these effects were independent of prepulse interval (all $P<.01$ for 30-, 60-, and 120-millisecond intervals). Error bars indicate SEM. † $P<.005$ vs no AP. ‡ $P<.001$ vs no AP. B, Mean startle magnitude on pulse-alone and combined prepulse and pulse trials in patients not receiving atypical APs and case-matched NCSs; groups were balanced precisely for startle magnitude on pulse-alone trials by omitting 1 subject whose startle magnitude on pulse-alone trials was 4.3 SDs above the group mean. Error bars indicate SEM. Analysis of variance of PPI percentage across these groups revealed a significant main effect of diagnosis ($F_{1,34}=7.39, P<.02$) († in inset) and no sex \times diagnosis interaction ($F_{1,34}=3.05, P>.05$). Analysis of variance of startle magnitude revealed a significant main effect of trial types ($F_{3,99}=35.77, P<.001$) and a significant interaction of diagnosis \times trial type ($F_{3,99}=5.21, P<.003$). Analysis of variance limited to prepulse trials revealed significantly greater startle magnitude on prepulse trials in patients than in NCSs ($F_{1,40}=15.60, P<.001$), reflecting a loss of sensorimotor inhibition. *Significantly greater startle on prepulse + pulse trials in patients than in NCSs after significant interaction of diagnosis \times trial type by Fisher protected least-significant difference.

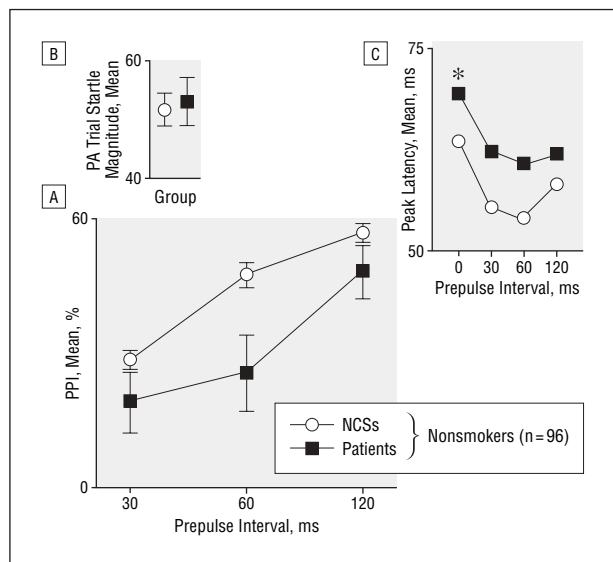


Figure 3. Smoking effects on startle measures. A, Mean prepulse inhibition (PPI) percentage in nonsmoking patients ($n=32$) and normal comparison subjects (NCSs) ($n=61$). Analysis of variance revealed a significant main effect of diagnosis ($F_{1,89}=13.20, P<.001$). A significant interaction of smoking \times medication (atypical antipsychotic vs no atypical antipsychotic) ($P<.02$) reflected PPI-enhancing effects of atypical antipsychotics among lighter smokers ($P<.008$) that were obviated by elevated levels of PPI among heavier smokers. There were no group difference in startle magnitude on pulse-alone (PA) trials (B) and slower reflex latency in patients ($*P<.001$) (C), as also shown in Figure 1. Subjects abstained from smoking for at least 20 minutes prior to testing. Error bars indicate SEM.

diagnosis \times sex \times interval; startle magnitude and latency were comparable to those in Figure 1 (Figure 3B and C). Among patients, ANOVA of PPI based on a median split of self-reported nicotine use (≤ 0.5 pack/d vs > 0.5 pack/d) revealed significantly higher PPI among heavier smokers ($F_{1,99}=10.20, P<.002$). A significant interaction of smoking \times medication (atypical AP vs no atypical AP) ($P<.02$) reflected PPI-enhancing effects of atypical APs among lighter smokers ($P<.008$) that were obviated by elevated levels of PPI among heavier smokers.

CLINICAL SYMPTOMS

Regression analyses revealed no significant correlations of PPI percentage (at 60 milliseconds) with SANS or SAPS scores or with combined SANS and SAPS scores ($0.00 < \text{all } r < 0.06$). Owing to the presence of some extreme values in measures of PPI at 60 milliseconds, these findings were confirmed using a Spearman rank analysis ($0.00 < \rho < 0.06$). Because multiple factors apparently influenced PPI in this sample (Figure 4), different approaches were used to isolate potential relationships between symptom severity and PPI. First, based on a significant difference in PPI in male patients vs female patients (43.73% vs 21.39%, respectively; $P<.03$), separate analyses conducted in men and women detected no significant correlations between symptom scale scores and PPI percentage. Next, comparing PPI percentage among subjects with the lowest vs highest quartile of SANS scores, SAPS scores, and combined SANS and SAPS scores as well as comparing clinical scores among subjects with the lowest vs highest quartile of PPI percentage revealed no sig-

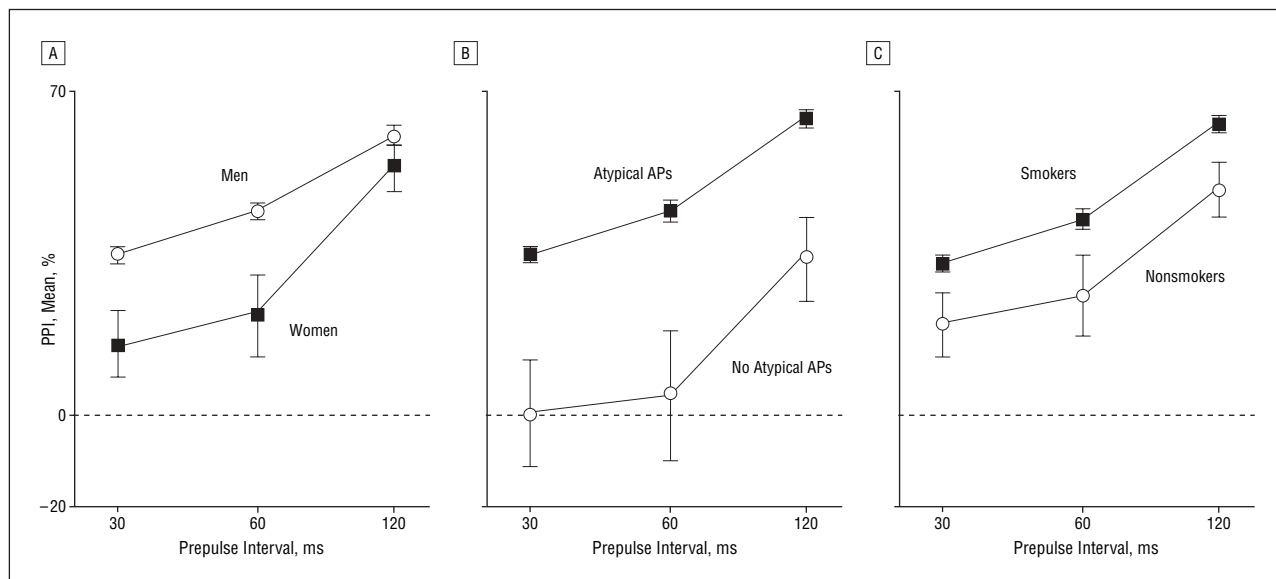


Figure 4. Summary figures showing significant differences in mean prepulse inhibition (PPI) percentage in 103 patients with schizophrenia based on sex (PPI in men > PPI in women; $P < .03$) (A), medications (PPI with atypical antipsychotic medications [APs] > PPI with no atypical APs; $P < .001$) (B), and smoking (PPI in smokers > PPI in nonsmokers; $P < .05$). Error bars indicate SEM.

nificant differences. Similar approaches limited to male or female patients not receiving atypical APs ($n = 18$; male:female ratio, 10:8) or nonsmokers ($n = 32$; male:female ratio, 26:6) yielded no significant relationships between symptom severity and PPI. Finally, ANOVAs of PPI using a median score split of each SANS and SAPS subscale detected no significant relationship between PPI and low vs high scores.

NEUROCOGNITIVE MEASURES

Studies^{42,66} have reported a weak or no relationship between neurocognitive performance and PPI in NCSs. We examined this relationship in patients and NCSs using the prepulse interval that detected maximal deficits (60 milliseconds) (Table 3). Parametric and nonparametric correlations revealed no significant relationships between PPI percentage and performance in any of the 17 primary neurocognitive variables. As with measures of clinical symptoms and function, we compared test scores in patients among the lowest vs highest quartiles of PPI percentage, and we compared PPI percentage among patients with the lowest vs highest quartiles of neurocognitive scores. These 34 quartile analyses revealed no significant differences.

Next, we assessed the relationship between neurocognitive performance and PPI among patients, separated from the effects of sex, medication, and smoking. Parametric and nonparametric correlations revealed no significant relationships between PPI percentage and any neurocognitive measure among 5 relevant subgroups of adequate size to test these relationships: (1) men; (2) women; (3) patients not receiving atypical APs; (4) nonsmokers; and (5) nonsmoking men (all $P > .20$). Median and quartile split analyses of PPI and neurocognitive measures also revealed no significant associations of higher PPI with higher neurocognitive performance among these 5 patient subgroups. In total, no signifi-

cant relationship between PPI and neurocognitive performance was detected in more than 300 comparisons.

FUNCTIONAL MEASURES

Relationships between PPI deficits and GAF scale, UPSA scale, and SOF scores were first tested via parametric and nonparametric correlations and then by quartile analyses as performed for symptoms and neurocognitive scores. The relationship between LIL scale scores and PPI was tested among the extreme quartiles of PPI percentage using χ^2 and Mann-Whitney U tests. Regression analyses using the full sample of 103 patients revealed no significant correlations of PPI percentage with GAF scale, SOF, or UPSA scale scores. However, Spearman rank analysis revealed a significant correlation between PPI percentage and GAF scale score ($P < .03$) but not between PPI percentage and either SOF score or UPSA scale score; categorical comparisons revealed significantly higher GAF scale (but not UPSA scale or SOF) scores among patients in the highest quartile of PPI percentage than among those in the lowest quartile ($P < .05$). Patients in the highest vs lowest quartile of PPI percentage differed significantly in their LIL scale scores: 61.50% of patients in the upper PPI quartile lived independently compared with 30.77% of the patients in the lower PPI quartile ($\chi^2 = 5.53$, $P \leq .02$; $U = 229$, $P < .05$).

We followed the same algorithm as described earlier to isolate a possible relationship between functional measures and PPI, separate from the influences of sex, medications, and smoking. Parametric and nonparametric correlations in male and female patients detected significant relationships between GAF scale scores and PPI percentage in men ($r = 0.28$, $P < .02$; $\rho = 0.341$, $P = .004$) (Figure 5A) but not women. Stratifying men based on GAF scale scores, ANOVA of PPI yielded a significant effect of GAF scale scores ($P < .002$) (Figure 5B). Analysis of variance of GAF scale scores in patients in the highest vs lowest quartile of PPI percentage confirmed a sig-

nificant interaction of sex \times quartile ($P < .003$). The GAF scale scores were significantly greater among men in the highest quartile of PPI percentage than among men in the lowest quartile ($P < .01$), and the inverse relationship (higher PPI percentage among men in the higher GAF scale score quartile) was also highly significant ($P < .001$) (Figure 5C).

Analyses limited to the small number of male ($n = 10$) or female ($n = 8$) patients who were not receiving atypical APs detected no significant correlations between GAF scale scores and PPI percentage. Among nonsmokers, only the subgroup of male patients was adequately large for meaningful statistical analysis ($n = 26$). In these patients, the correlation of GAF scale scores and PPI percentage approached significance ($r = 0.38$, $P < .06$). Median split analysis revealed significantly higher PPI in patients with higher GAF scale scores ($P < .02$); the inverse relationship (higher GAF scale scores among patients with higher PPI scores) reached significance when comparing the extreme quartiles ($P < .02$).

COMMENT

This study detected reduced PPI in a large cohort of patients with schizophrenia compared with NCSs. This deficit was statistically significant but small ($d = 0.24$) and limited to 60-millisecond prepulse intervals. Strikingly, this deficit was substantially more pronounced and evident at all prepulse intervals when comparisons were limited to patients who were not receiving atypical APs or were nonsmokers. Prepulse inhibition was sexually dimorphic among patients with schizophrenia (PPI in men $>$ PPI in women), as previously reported in NCSs.^{34,42-45} The PPI deficits in patients were not related to clinical symptoms or performance on several neurocognitive measures, but—particularly among male patients—these deficits were significantly related to 2 measures of long-term function.

Deficits in the automatic sensorimotor gating of startle have been described in patients with schizophrenia by many different groups.³⁵ A small number of studies have failed to detect PPI deficits in patients with schizophrenia using stimulus conditions (eg, low background noise and very high prepulse intensities relative to background) that differ substantially from those used in studies that detect deficits.^{35,67,68} Also, many studies describing sensorimotor gating deficits in patients with schizophrenia vs NCSs have been inadequately powered to assess the potential impact of moderating variables on patterns of PPI deficits. The relevance of these moderating factors, including sex, APs, and nicotine, is underscored by findings in both preclinical and normal human studies.^{19,20,23,42-45,64,69-71}

Sex differences and menstrual cyclicity in PPI described by several different groups^{34,42-45,72} have important implications for the interpretation of PPI differences in schizophrenia vs NCS populations. As in the present study, open recruitment typically favors ascertainment of male patients and female NCSs. Because men exhibit more PPI than women, this ascertainment bias artificially diminishes NCS vs schizophrenia group differences. Menstrual cyclicity of PPI adds uncontrolled vari-

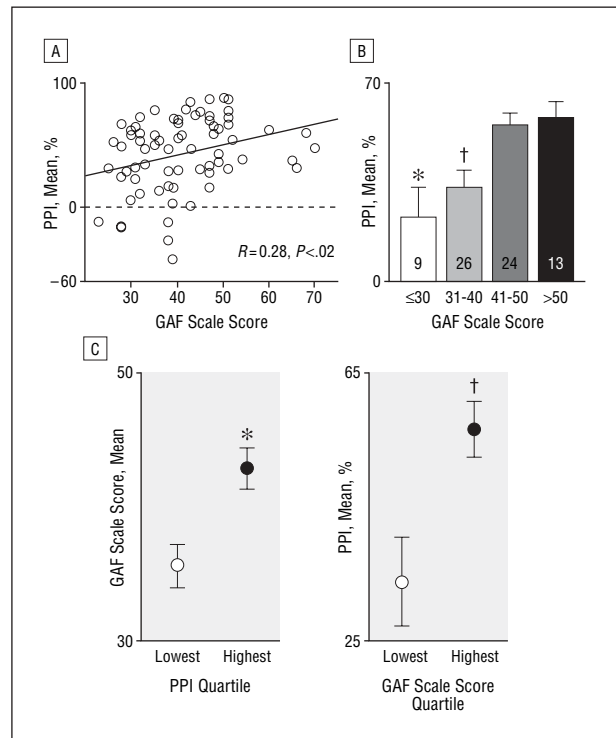


Figure 5. Relationship between mean (SEM) prepulse inhibition (PPI) percentage at a 60-millisecond interval and measures of function in male patients. Compared with normal comparison subjects, patients were significantly impaired as assessed by the Global Assessment of Functioning (GAF) scale and the Level of Independent Living scale (Scale of Functioning and University of California, San Diego, Performance-based Skills Assessment scale scores were not collected from normal comparison subjects) (Table 2). None of the 4 measures of function differed significantly among patients based on sex or medication status. Heavier smokers were more likely to live in structured or semistructured settings ($P < .05$) and have lower Scale of Functioning scores ($P < .02$). A, Regression analysis shows higher GAF scale scores associated with higher PPI percentages. B, Categorical comparison using analysis of variance shows an orderly increase in PPI across categories of increasing GAF scale scores. * $P < .004$ vs “41-50” and vs “ > 50 .” † $P < .01$ vs “41-50” and vs “ > 50 ” by Fisher protected least-significant difference. Numbers in each bar indicate the sample size; error bars, SEM. C, Comparisons using extreme quartiles. There were significantly greater GAF scale scores among patients in the highest quartile of PPI scores as compared with those in the lowest quartile (* $P < .01$) and significantly greater PPI percentages among patients in the highest quartile of GAF scale scores as compared with those in the lowest quartile († $P < .001$). Similar comparisons between PPI and Scale of Functioning or University of California, San Diego, Performance-based Skills Assessment scale scores in men (all or nonsmoking) detected no significant relationships, although in each of the 24 comparisons, the relationship was in the direction of greater PPI associated with better functional performance. Examination of the individual subscales among men revealed significant Spearman rank correlations between PPI and 4 Scale of Functioning items—orientation ($P < .02$), keeps appointments ($P < .02$), formulates realistic plans ($P < .05$), and less overall impairment ($P < .04$)—as well as the University of California, San Diego, Performance-based Skills Assessment subscale household chores ($P < .03$). Comparisons of PPI and Level of Independent Living scale scores in this group revealed significantly greater PPI among the most-independent functioning subjects as compared with the least-independent functioning subjects ($P < .05$) and significantly more independent living among subjects in the highest PPI quartile as compared with those in the lowest PPI quartile ($\chi^2 = 6.47$, $P < .02$). Error bars indicate SEM.

ance that may differentially affect NCS vs patient samples based on hormonal effects of APs.⁴⁸ Nevertheless, PPI deficits have been described in both male and female patients with schizophrenia.^{18,30} Lower PPI in female patients as compared with PPI in male patients has implications for studies attempting to assess clinical or functional correlates of PPI in schizophrenia: sex differ-

ences in PPI among patients may obscure the impact of many other moderating variables or correlates.

The initial report⁵ of PPI deficits in patients with schizophrenia predated the use of atypical APs. Preclinical studies later demonstrated that in addition to preventing the PPI-disruptive effects of various experimental manipulations, atypical APs also enhance baseline PPI in some rodent strains and species.¹² Subsequent clinical reports^{19,20,23,73} have suggested that atypical APs are associated with greater and potentially normalized PPI levels in patients with schizophrenia. In the present study, only 17% of patients were not being treated with atypical APs. Clearly, if atypical APs increase PPI in some groups of patients, the result of such pervasive use of atypical APs in patients with schizophrenia (or other populations, eg, patients with Tourette syndrome^{74,75}) will be to diminish or eliminate the ability to detect PPI deficits between patients and NCSs. The present findings support the notion that PPI deficits in patients with schizophrenia can be masked by atypical APs. Some studies^{20,73} also suggest that these deficits are partially normalized by typical APs, and the present findings are consistent with these articles (Figure 2A). Because an overwhelming number of patients with schizophrenia are currently treated with atypical APs, it is possible that PPI deficits in this population are a vanishing biomarker. Alternative strategies for understanding the biology and clinical implications of deficient sensorimotor gating have become increasingly important, including the use of optimized stimulus features (eg, 60-millisecond prepulse intervals [see later], broadband stimuli, and prominent background noise²¹), unmedicated patients with schizophrenia^{25,29} and schizophrenia spectrum,^{36,37} and populations of low-gating NCSs.⁷⁶

Antipsychotic medication use was not associated with reduced startle magnitude in this study. Short-term administration of APs depresses startle in rodents¹¹ and humans³⁵ whereas startle-reducing effects of sustained AP exposure are less consistent.^{35,77}

Progating effects of nicotine are described in measures of both PPI and P50 event-related potential suppression.^{62-64,78,79} If nicotine use per se is associated with increased PPI, then greater smoking among patients with schizophrenia would be expected to diminish group differences in PPI measures. However, nicotine has complex pharmacological effects characterized by rapid shifts in both blood levels and states of receptor sensitization that can influence PPI.^{41,64,70} Because studies cannot easily control for the time interval between PPI testing and smoking, the amount smoked, smoking history, or the interindividual differences in nicotine receptor sensitivity, the impact of smoking on PPI is to increase uncontrolled variance. In this study, adequate power to compare nonsmoking patients (particularly men) vs nonsmoking NCSs revealed group PPI differences (PPI in NCSs > PPI in patients) with greater group separation than was observed across the inclusive group of smokers and nonsmokers. Furthermore, among patients, PPI was significantly greater among heavier smokers.

Despite the potent PPI-enhancing effects of atypical APs and nicotine in patients with schizophrenia, PPI deficits at the 60-millisecond prepulse interval were detect-

able in the full cohort of 103 patients. This pattern suggests that PPI deficits at the 60-millisecond interval are most resistant to the normalizing effects of APs and nicotine, consistent with the fact that 60 milliseconds is the interval at which PPI deficits are most often reported in medicated patients with schizophrenia.^{5,14,20,23,30,35} Studies⁸⁰⁻⁸² have described differences in the sensitivity of short- vs long-interval PPI to specific pharmacological interventions in rats, and it is conceivable that the 60-millisecond interval might be one that is least sensitive to progating effects of certain neurochemical influences in humans. Reflex inhibition 60 milliseconds after a prepulse appears to be regulated by processes at the boundary between automatic and attentionally sensitive inhibition.⁸³ In other words, this temporal domain of inhibition sits at a transitional point between information that is regulated automatically and that which can be manipulated volitionally. Theoretical models have proposed that this transitional zone between consciously accessible and unconscious processing is of particular importance for regulating the contents of consciousness and may also be an epoch of particular vulnerability in psychopathological states.^{6,84-88} The fact that sensorimotor gating at 60-millisecond prepulse intervals remains impaired (as do function and quality of life) despite the impact of atypical APs and nicotine suggests that gating at this interval may be of particular importance to the biology of schizophrenia.

Studies^{18,34,35} have reported weak or no correlations between symptom severity and PPI in patients with schizophrenia. Smaller studies from our group have either detected¹⁸ or failed to detect⁸⁹ significant correlations between PPI percentage and SAPS and SANS scores in male patients with schizophrenia. With the large cohort of patients in this study, no simple relationship could be detected between PPI and positive or negative symptom severity or age among the full sample or in subgroups of nonsmokers and patients not receiving atypical APs. Certainly, there are many symptoms of schizophrenia that are not the focus of the SAPS or SANS that might correlate significantly with PPI.^{89,90}

A preliminary qualitative article by Butler et al⁹¹ noted a trend toward greater tactile (but not acoustic) PPI among 6 (predominantly male) patients with schizophrenia and low levels of Wisconsin Card Sorting Test perseverative responses than among 9 (predominantly female) patients distinguished by high levels of Wisconsin Card Sorting Test perseverative responses. We observed no such trend with acoustic PPI in the present study. Karper et al⁹⁰ reported a significant negative correlation between right-eye-blink 120-millisecond acoustic PPI and lateralized attention in a Posner task, and Perry and Braff⁸⁹ reported a significant negative correlation between right-eye-blink 120-millisecond acoustic PPI and a Rorschach-based measure of thought disorder. The lack of Posner and Rorschach measures in the present study makes it difficult to compare those findings with our own. Nonetheless, our failure to detect a relationship between PPI and performance across neurocognitive measures was not for lack of trying; numerous strategies were used to try to find some association of PPI and neurocognition. At least 2 conclusions follow from these definitively nega-

tive findings. First, the information yielded by these neuropsychological measures is not redundant with that detected by measures of automatic sensorimotor gating. Second, among a large cohort of patients with schizophrenia, brain circuitry responsible for deficits in sensorimotor gating does not contribute via a strong path to deficits in these neuropsychological measures. If we posit that PPI deficits in patients with schizophrenia reflect abnormal activity within a particular brain circuit, we would predict that these PPI deficits should correlate positively with deficits in other normal functions of that circuit. Despite substantial power afforded by this large cohort (a sample of 100 detects a significant [$\alpha=0.05$] correlation of moderate effect size [$r=0.30$] with power [$\beta \approx 0.90$]),⁶¹ no such significant correlation was detected between PPI and neurocognitive measures.

A significant relationship with PPI was detected with 2 functional measures across the entire cohort of patients: the GAF scale and the LIL scale. Significant relationships between PPI and GAF scale scores were evident only in nonparametric or categorical analyses using ranks or extreme quartiles of PPI. Similarly, the relationship between low PPI scores and limited independence of living was detected only among the extreme quartiles of PPI. Given the sensitivity of PPI to a number of potentially confounding moderating factors, it is striking that any relationship could be detected between PPI and global measures of functioning among this heterogeneous group of patients. For example, the least-independent patients (who had the lowest PPI) were the heaviest smokers, and heavier smoking was associated with higher PPI. Not surprisingly, few robust relationships have been identified in the literature between functioning and performance in a wide range of neurocognitive and electrophysiological measures.^{92,93}

In sharp contrast, when analyses were restricted to male patients, the relationships between PPI and scores on the GAF and LIL scales were relatively robust and consistent: higher PPI was associated with better functioning. Because both the GAF scale and the LIL scale use a single score, it was not possible to characterize the specific domains of functional strengths—beyond the important ability to live independently—that were associated with higher levels of PPI in male patients. However, both the SOF and UPSA scale involve composite ratings, and post hoc exploratory analyses suggested positive relationships with PPI: the abilities to keep appointments, formulate realistic plans, and complete household chores. These skills would appear to share common elements of effective sequencing or planning, which were not assessed directly by any of the neurocognitive measures in the present test battery. Because PPI deficits did not correlate significantly with these neurocognitive measures, the associations between function and neurocognition on the one hand (Table 3) and between function and sensorimotor gating on the other (Figure 5) appear to reflect different and perhaps independent pathways.

A reduction in the motor-inhibitory effectiveness of prepulses is seen clearly in the present study among patients not receiving atypical APs (Figure 2B). A similar observation was made in the first article⁵ describing PPI deficits in patients with schizophrenia. At an empirical

level, this finding demonstrates that for 30 to 120 milliseconds after stimulation, the central nervous system in patients with schizophrenia is more responsive to a second stimulus than the central nervous system in normal individuals. At a conceptual level, this state of deficient time-locked, automatic inhibition might put the information contained in the initial stimulus at greater risk to be degraded and therefore to not enter a hierarchical process that would lead to its appropriate cognitive or behavioral consequence. We do not know the real-world consequences of inhibitory deficits detected in laboratory measures of PPI, but evidence suggests that in some cases, PPI deficits might reflect processes associated more generally with a loss of protection of cognitive, sensory, or motor information.^{74,89,94,95} The present findings confirm that in patients with schizophrenia, PPI deficits are associated with specific measures of global, longstanding functional impairment.

Slowed reflex latency among patients with schizophrenia has not been uniformly detected in other studies^{5,14,18} but has been detected in other chronic neuropsychiatric disorders.⁹⁴ The strong positive relationship between latency and age in patients but not NCSs suggests that relatively caudal portions of the acoustic startle circuitry might be sensitive to processes associated with the chronicity of schizophrenia—either direct effects of the illness or sustained exposure to medications. Changes associated with increased latency in patients appear to be distinct from those associated with reduced PPI because these variables do not correlate significantly in patients and are related to different clinical factors (PPI: smoking, medications, functional status; latency: age, SAPS score), although both variables are sexually dimorphic (PPI in men > PPI in women; latency in women > latency in men).

The ability to detect PPI deficits in patients with schizophrenia is greatly enhanced by strategies that remove sources of uncontrolled variance (eg, sex differences and uncontrolled effects of menstrual cyclicity on PPI) and that exclude factors known to enhance PPI (eg, atypical APs and nicotine use). Future studies using PPI as a biomarker for neurobiological studies or as an endophenotype for genetic analyses need to carefully consider these moderating variables, together with the known sensitivity of PPI to stimulus parameters and experimental conditions, to maximize the utility of PPI for understanding the neurobiology, genetics, and treatment of schizophrenia.

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Correction

Errors in Table and Figure. In the Original Article titled "Startle Gating Deficits in a Large Cohort of Patients With Schizophrenia: Relationship to Medications, Symptoms, Neurocognition, and Level of Function," published in the December 2006 issue of the ARCHIVES (2006;63:1325-1335), there are errors in Table 2 and Figure 2A. In Table 2, the third entry under the column heading "Characteristic" should have read, "Psychiatric hospitalizations, mean (range), No." In Figure 2A, the lengths of the error bars have been corrected. The corrected **Figure 2** and its legend are printed here in their entirety.

Figure 2. Medication effects on prepulse inhibition (PPI) in patients. A, Mean PPI percentage collapsed across prepulse intervals in patients treated with no antipsychotic medication (AP), typical APs, atypical APs, or both typical and atypical APs. Mean PPI percentage for normal comparison subjects (NCSs) are shown as a single point. Analysis of variance of PPI percentage in patients revealed a significant main effect of medication subgroups ($F_{3,95}=7.52, P<.001$), which was also significant when limited to 60-millisecond prepulse intervals ($F_{3,99}=6.06, P<.001$). Compared with PPI among NCSs, PPI was significantly reduced among unmedicated patients ($*P<.001$ by Fisher protected least-significant difference) and among all patients not receiving an atypical AP ($P=.001$); these effects were independent of prepulse interval (all $P<.01$ for 30-, 60-, and 120-millisecond intervals). Error bars indicate SEM. † $P<.005$ vs no AP. ‡ $P<.001$ vs no AP. B, Mean startle magnitude on pulse-alone and combined prepulse and pulse trials in patients not receiving atypical APs and case-matched NCSs; groups were balanced precisely for startle magnitude on pulse-alone trials by omitting 1 subject whose startle magnitude on pulse-alone trials was 4.3 SDs above the group mean. Error bars indicate SEM. Analysis of variance of PPI percentage across these groups revealed a significant main effect of diagnosis ($F_{1,34}=7.39, P<.02$) († in inset) and no sex \times diagnosis interaction ($F_{1,34}=3.05, P>.05$). Analysis of variance of startle magnitude revealed a significant main effect of trial types ($F_{3,99}=35.77, P<.001$) and a significant interaction of diagnosis \times trial type ($F_{3,99}=5.21, P<.003$). Analysis of variance limited to prepulse trials revealed significantly greater startle magnitude on prepulse trials in patients than in NCSs ($F_{1,40}=15.60, P<.001$), reflecting a loss of sensorimotor inhibition. *Significantly greater startle on prepulse + pulse trials in patients than in NCSs after significant interaction of diagnosis \times trial type by Fisher protected least-significant difference.

