ORIGINAL ARTICLE

Effects of γ-Aminobutyric Acid–Modulating Drugs on Working Memory and Brain Function in Patients With Schizophrenia

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Context: Cognitive impairment causes morbidity in schizophrenia and could be due to abnormalities of cortical interneurons using the inhibitory neurotransmitter γ-aminobutyric acid (GABA).

Objectives: To test the predictions that cognitive and brain functional responses to GABA-modulating drugs are correlated and abnormal in schizophrenia.

Design: Pharmacological functional magnetic resonance imaging study of 2 groups, each undergoing scanning 3 times, using an N-back working memory task, after placebo, lorazepam, or flumazenil administration.

Setting and Participants: Eleven patients with chronic schizophrenia were recruited from a rehabilitation service, and 11 healthy volunteers matched for age, sex, and premorbid IQ were recruited from the local community.

Intervention: Participants received 2 mg of oral lorazepam, a 0.9-mg intravenous flumazenil bolus followed by a flumazenil infusion of 0.0102 mg/min, or oral and intravenous placebo.

Main Outcome Measures: Working memory performance was summarized by the target discrimination index at several levels of difficulty. Increasing (or decreasing) brain functional activation in response to increasing task difficulty was summarized by the positive (or negative) load response.

Results: Lorazepam impaired performance and flumazenil enhanced it; these cognitive effects were more salient in schizophrenic patients. Functional magnetic resonance imaging demonstrated positive load response in a frontoparietal system and negative load response in the temporal and posterior cingulate regions; activation of the frontoparietal cortex was positively correlated with deactivation of the temporocingulate cortex. After placebo administration, schizophrenic patients had abnormally attenuated activation of the frontoparietal cortex and deactivation of the temporocingulate cortex; this pattern was mimicked in healthy volunteers and exacerbated in schizophrenic patients by lorazepam. However, in schizophrenic patients, flumazenil enhanced deactivation of the temporocingulate and activation of the anterior cingulate cortices.

Conclusions: The GABA-modulating drugs differentially affect working memory performance and brain function in schizophrenia. Cognitive impairment in schizophrenia may reflect abnormal inhibitory function and could be treated by drugs targeting GABA neurotransmission.

Arch Gen Psychiatry. 2007;64:156-167

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IMPAIRMENTS IN EXECUTIVE FUNCTION and memory are major impediments to social rehabilitation and predict poor clinical outcome in patients with schizophrenia (hereafter referred to as schizophrenic patients).[1-5] Cognitive deficits in schizophrenia are traitlike and heritable, but their neurobiological basis and a rationale for targeted pharmacological intervention are not clear.[6-10] Despite the success of antipsychotic drugs in treating positive symptoms, lack of effective pharmacotherapy for cognitive symptoms remains a major unmet need in the management of schizophrenia.

One hypothesis concerning the neurobiological substrate of cognitive deficits in schizophrenia highlights the role of inhibitory cortical interneurons using γ-aminobutyric acid (GABA) as their main transmitter.[11-13] The GABA interneurons are increasingly recognized as important for coordinating synchronized oscillations in sparse assemblies of pyramidal neurons; such oscillations are a plausible physiological substrate for perception, memory, and cognition and show alterations in schizophrenia.[14-24] There is abundant histopathological evidence of abnormalities in GABA neurons and their postsynaptic receptors in the prefrontal and anterior cingulate cortices of schizophrenic patients.[25-31] These observations predict that drugs modulating inhibitory transmission via $GABA_A$ receptors could be relevant in treating cognitive deficits in schizophrenia.[12,32] Previously published data indicate some therapeutic potential

Table 1. Demographic Characteristics of Schizophrenic Patients and Matched Healthy Volunteers Participating in a Pharmacological fMRI Study of Working Memory

Characteristic	Healthy Volunteers (n = 11)		Schizophrenic Patients (n = 11)		*t**	*P* Value
	Mean (SD)	Range	Mean (SD)	Range		
Age, y	41.0 (6.0)	29-50	44.4 (11.1)	24-65	−0.89	.39
NART score	108 (11.0)	90-124	105 (7.6)	94-117	0.84	.41
RBMT score	23.1 (1.4)	20-24	18.1 (3.5)	12-23	4.34	<.001
Verbal fluency†	17.3 (5.8)	10-32	12.1 (4.2)	8-18.5	2.31	.03

Abbreviations: fMRI, functional magnetic resonance imaging; NART, National Adult Reading Test; RBMT, Rivermead Behavioral Memory Test.
*For age, *df* = 20; for the NART and RBMT scores and verbal fluency, *df* = 19 because results of the NART, RBMT, and verbal fluency were unavailable for 1 participant.
†Verbal fluency was assessed by (1) generation of exemplars within 1 minute from a semantic category and (2) generation of exemplars within 1 minute from a given starting letter.

for benzodiazepines in the treatment of positive and negative psychotic symptoms,[33,34] but the effects of GABA-modulating drugs on cognition in schizophrenic patients have not been addressed previously.

To investigate this, we measured task performance and brain functional activation while schizophrenic patients performed a working memory task during functional magnetic resonance imaging (fMRI). Working memory is robustly impaired in schizophrenia,[35-37] and we used a paradigm well known to activate the frontal and cingulate regions where interneuronal abnormalities have been described in schizophrenia.[25,26,32,38,39] During 3 fMRI sessions at 2-week intervals, each participant repeated the task 3 times after acute dosing with placebo, lorazepam, or flumazenil. Lorazepam is an agonist at the $GABA_A$ receptor benzodiazepine site, where it allosterically enhances postsynaptic inhibitory effects; it is used widely in treating anxiety symptoms. Flumazenil is an antagonist or a partial inverse agonist at the $GABA_A$ receptor benzodiazepine site.[40-42] Although used clinically as an antidote for respiratory failure due to sedative benzodiazepine poisoning, evidence indicates that flumazenil may affect cognition in humans and animals and even enhance learning and memory.[43-45]

We hypothesized that if cognitive deficits in schizophrenia[1,2,5] were due to GABA interneuron abnormalities,[11,25-27,30,32,46] working memory performance would be differentially modulated by drugs affecting transmission at the $GABA_A$ receptors in schizophrenic patients compared with healthy volunteers; for example, selectively impaired by lorazepam in the patients. We also predicted that the functional effects of drug treatment in the brain would be correlated with cognitive effects and would be abnormal in schizophrenic patients.

METHODS

SAMPLE

Twelve male right-handed patients with an operational *DSM-IV*[47] diagnosis of schizophrenia and 12 male right-handed healthy volunteers matched with patients for age and premorbid IQ (measured using the National Adult Reading Test)[48] participated in the study (**Table 1**). Healthy volunteers were recruited by advertisement from the local population. Schizophrenic patients were recruited by a consultant psychiatrist from a clinical rehabilitation service for patients with chronic psychosis in Cambridge, England. Additional clinical data are given in **Table 2**. All participants were screened to exclude psychiatric or neurological disorders (other than schizophrenia in the patients), head injury, history of substance abuse, current medication (in particular, benzodiazepines or anticholinergic drugs) with the exception of antipsychotics in the patient group, and contraindications to MRI. All participants had negative urinalysis findings for illicit drug metabolites when recruited and were screened for episodic memory and executive function using the Rivermead Behavioral Memory Test[49] and a verbal fluency test (Table 1).

One patient was excluded after failure to perform the task during MRI. To maintain a balanced design for factorial analysis (important in ensuring that interaction effects remain orthogonal) and to allow permutation testing of the imaging data,[50-52] 1 volunteer was also excluded at random, leaving 11 patients and 11 control subjects for behavioral and imaging analysis. A secondary analysis of the behavioral data, including the 12th volunteer, is also reported in the supplemental material (available at http://www-bmu.psychiatry.cam.ac.uk/data/menzies).

The study was approved by the local research ethics committee of Addenbrooke's Hospital, Cambridge, and the Medicines Control Agency, London, England. After a complete description of the study, written informed consent was obtained from all participants. The participants were paid an honorarium and travel expenses.

STUDY DESIGN AND DRUG TREATMENTS

We used a placebo-controlled, randomized, double-blind, balanced factorial design with drug treatment as a within-subject factor and diagnostic group as a between-subjects factor. Each participant underwent MRI on 4 occasions at 2-week intervals. Structural MR images were acquired during the first session, which also acclimated participants to the scanner and experimental task. In the remaining 3 sessions, participants were assigned to 1 of 3 treatments: placebo, intravenous (IV) flumazenil, or oral lorazepam. To control for task practice effects entailed by the repeated-measures design, the order of drug administration was counterbalanced across participants. One patient's data after placebo administration only were unavailable; mean values were imputed where appropriate.

Lorazepam and flumazenil are widely used clinically and were well tolerated by our study participants. Drug doses and timings were selected on the basis of published pharmacokinetic data.[53] To control for different modes of drug administration, we used the following regimen: 120 minutes before all MRI sessions, participants received an oral capsule, and 10 minutes be-

Table 2. Clinical Characteristics of Schizophrenic Patients

Patient No.	Medication	Daily Dose, mg	Duration of Illness, y	Score		
				SANS	SAPS	BPRS
1	Clozapine	200-400	20	16	8	54
	Propranolol hydrochloride	40				
2	Clozapine	87.5	5	11	4	52
	Propranolol	As required				
3	Clozapine	200	19	10	1	48
4	Clozapine	550	27	9	8	48
5	Clozapine	600	19	13	6	52
	Chlorpromazine hydrochloride	100				
6	Clozapine	200	17	18	7	63
	Lithium carbonate	800				
7	Clozapine	225	15	5	0	42
8	Clozapine	400	7	12	7	50
	Sulpiride	200-400				
9	Clozapine	200-300	7	5	1	50
	Haloperidol decanoate	10 BID				
10	Olanzapine	10	32	17	3	52
11	Clozapine	100	19	NA	NA	NA
Mean (SD) findings			17.0 (8.3)	11.6 (4.6)	4.5 (3.1)	51.1 (5.3)

Abbreviations: BID, twice daily; BPRS, Brief Psychiatric Rating Scale; NA, not available; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms.

fore MRI they were administered a 10-mL IV bolus followed by an IV infusion until the MRI session was finished (approximately 90 minutes later). In the placebo condition, the oral tablet contained lactose, and the IV bolus and infusion contained isotonic sodium chloride solution. In the lorazepam condition, the oral capsule contained 2 mg of lorazepam, and the IV bolus and infusion contained isotonic sodium chloride solution. In the flumazenil condition, the oral capsule contained lactose, but the IV bolus contained 0.9 mg of flumazenil, and the infusion delivered flumazenil at a rate of 0.0102 mg/min, calculated to maintain steady plasma levels.

N-BACK WORKING MEMORY TASK

The N-back test of verbal working memory was presented at 3 levels of difficulty in a blocked periodic paradigm.[38,39] At the easiest level, N=1, subjects were asked to indicate when the current letter in a series of visually presented letters was the same as the immediately preceding one; at more difficult levels, N=2 or N=3, subjects were asked to indicate when the current letter was the same as that presented 2 or 3 trials earlier. Subjects were also asked to perform a sensorimotor control task, N=0, in which they had to indicate whether the current letter was *X*. The interstimulus interval (stimulus duration) was 2200 milliseconds; 13 stimuli were presented in each of 4 blocks at each level of difficulty (52 stimuli at each level of difficulty; 16 blocks in total). There were 3 or 4 target stimuli per block; that is, the probability of a target trial was 23% or 31%. Each block was preceded by a brief (2000-millisecond) visual cue to perform the task at a certain level of difficulty; the order of the blocks of trials at different difficulty levels was counterbalanced to control for nonspecific practice effects during the course of each experiment lasting 8 minutes and 10 seconds.

Performance was monitored behaviorally by a right-handed button press, with one button for targets and another for nontargets. A program for stimulus presentation and behavioral monitoring was written in DMDX.[54]

fMRI DATA ACQUISITION

Gradient-echo echoplanar imaging data depicting blood oxygen level–dependent contrast were acquired using a commercially available 3T MRI scanner (Bruker Medspec S300 System; Bruker, Etlinger, Germany) at the Wolfson Brain Imaging Centre of Addenbrooke's Hospital, Cambridge. During each acquisition, 454 images consisting of 21 near-axial slices were collected with the following settings: repetition time, 1100 milliseconds; echo time, 27.5 milliseconds; flip angle, 65°; slice thickness, 4 mm with an interslice gap of 1 mm; matrix size, 64×64; and in-plane resolution, 3.75 mm. The first 6 images, acquired before starting the working memory paradigm, were discarded to allow for T1 equilibrium, leaving 448 images available for analysis. To minimize problems of image-acquisition at 3T, for example, in the orbitofrontal and inferior temporal regions, all tests on imaging data were performed only at voxels where all subjects had a nonzero activation statistic, thus avoiding spurious results due to signal dropout.

BEHAVIORAL DATA ANALYSIS

We used a repeated-measures analysis of variance (ANOVA) to model within-subject effects of block repetition, task difficulty, drug treatment, and session order and the between-subjects effect of diagnostic group on task performance. Performance was measured using response latency and the discrimination index (Pr), a standard accuracy metric derived from signal detection theory. We calculated Pr=P/T−FP/N as the hit rate minus the false-positive rate, ie, the number of positive hits (correct identifications of a target [P]) divided by the total number of target trials (T) minus the number of false-positive trials (FP) divided by the total number of nontarget trials (N). To summarize overall accuracy of task performance at all levels of difficulty in the paradigm, we calculated the area under the curve (AUC) of Pr vs task difficulty. Greater AUC(Pr) indicates better task perfor-

mance with consideration of all difficulty levels. Nonresponses were excluded from calculation of the Pr index and response latency. Where necessary, the Huynh-Feldt epsilon algorithm was applied to correct for nonsphericity. Homogeneity of variance was checked by the Levene test, and we used post hoc *t* tests where appropriate.

fMRI DATA ANALYSIS

Each individual data set was preprocessed to correct for head motion effects,[55] detrended, and smoothed by a 2-dimensional Gaussian filter with a standard deviation of 1.875 mm. Positive or negative brain functional load response, defined as an increase or a decrease in brain activation linearly related to the 4 levels of increasing task difficulty, was estimated by regressing a hemodynamically convolved contrast on the movement-corrected time series at each voxel. For each participant, the resulting brain maps of the load response, normalized by the standard error of the load-response estimation at each voxel, were coregistered in the space of the Montreal Neurological Institute–echoplanar imaging template image using affine transformation.[56,57]

Considering first only data acquired from the healthy volunteers after placebo administration, we used a permutation test to identify voxels where the median load response was significantly greater (more strongly negative or positive) than under the null hypothesis that the median load response was not related to task performance. This analysis produced a map of the brain systems normally activated or deactivated by the N-back working memory task (**Figure 1**A).

We then explored group and drug effects on the load response in these systems in 2 ways. First, we used the normal activation and deactivation systems as a mask to define the mean load response across all voxels constituting these systems in data acquired from all participants after all treatments. This allowed us to describe the group and drug effects on load response at a systems level (**Figure 2**). Second, to localize the group and drug effects with greater anatomical resolution, we fitted a 2-way ANOVA model to the load-response statistics estimated at each voxel of the normal activation and deactivation systems and again used permutation testing to identify spatial clusters of voxels where there were significant group and drug effects.

Finally, we investigated the relationship between the cognitive and brain functional effects of drug treatment in 2 ways. First, we simply estimated the correlations between the summary performance metric, AUC(Pr), and the sum of the absolute mean load-response statistics in the activation and deactivation systems. Second, we regressed AUC(Pr) on the load-response statistics estimated at each voxel in standard space and identified, by permutation testing, voxels where there was significant psychophysiological association between the task performance and brain function (Figure 1B).

All statistical brain mapping was conducted nonparametrically using previously validated methods for permutation testing.[51,57] To control for type I (false-positive) error rates in the context of the statistical tests potentially entailed for brain mapping in fMRI, we used the following strategies: (1) 2-way ANOVA of group and drug effects was restricted to a reduced search volume defined by the normal activation and deactivation systems; (2) a cluster-level statistic (the sum of spatially contiguous voxel statistics exceeding a preliminary threshold) that we have previously shown increases sensitivity and reduces search volume was used for all analyses[51,58]; and (3) the *P* value for all maps was chosen such that the expected number of false-positive clusters was less than 1 cluster per map.

RESULTS

DEMOGRAPHIC, PSYCHOLOGICAL, AND CLINICAL CHARACTERISTICS

The 2 groups were well-matched by age and premorbid IQ; however, the schizophrenic patients had significant impairments on the memory and verbal fluency tests (Table 1). Clinically, the schizophrenic patients had a chronic disorder and were moderately symptomatic despite receiving antipsychotic drugs (most frequently, clozapine) (Table 2).

WORKING MEMORY TASK PERFORMANCE

Discrimination Index

Descriptive statistics on the discrimination index (Pr) stratified by level of difficulty, drug treatment, and diagnostic group are summarized in **Table 3**. The repeated-measures ANOVA demonstrated a main effect of task difficulty ($F_{3,60}=7.58$; $P<.001$) and a main effect of drug ($F_{2,40}=3.44$; $P=.04$). Across all of the participants, we found the expected decline in task performance as task difficulty increased and that the 2 drugs generally had opposing effects, with a tendency for improved performance after flumazenil administration and impaired performance after lorazepam administration. The post-hoc *t* tests of drug effects showed a significant performance impairment across all subjects after lorazepam compared with placebo administration ($t_{351}=3.29$; $P=.001$) but nonsignificant effects of flumazenil compared with placebo administration ($t_{351}=-1.12$; $P=.26$).

However, the behavioral effects of the drugs were clearly modulated by task difficulty and diagnostic status. There was a significant drug × difficulty interaction ($F_{5.5,109.2}=2.24$; $P=.05$), with the effects of the drug being particularly strong at the N = 1 and N = 2 levels of difficulty. Importantly, there was a group × drug interaction ($F_{2,40}=3.96$; $P=.03$) owing to greater, significant effects of lorazepam and flumazenil in schizophrenic patients compared with the nonsignificant effects of both drugs in healthy volunteers (see **Figure 3** for post hoc *t* tests). There was also a significant group × drug × difficulty interaction ($F_{5.5,109.2}=2.42$; $P=.04$), indicating that GABA-modulating drugs had differential effects on the cognitive load response in the schizophrenic patients compared with the healthy volunteers (Figure 3A).

There was no significant main effect of task repetition (practice) ($F_{2.3,46.3}=0.05$; $P=.37$) or session order ($F_{1.7,34.7}=1.36$; $P=.27$), nor was the order × group interaction ($F_{1.7,34.7}=0.07$; $P=.91$) significant, suggesting that pharmacological effects were not confounded by the order of drug administration and that counterbalancing of drug order between groups successfully controlled this potential bias.

Area Under the Task Performance Curve

To summarize each subject's behavioral response, their total working memory performance across all levels of task difficulty was calculated as the area under the task performance curve (AUC[Pr]) (Figure 3B and Table 3). For all of the drug

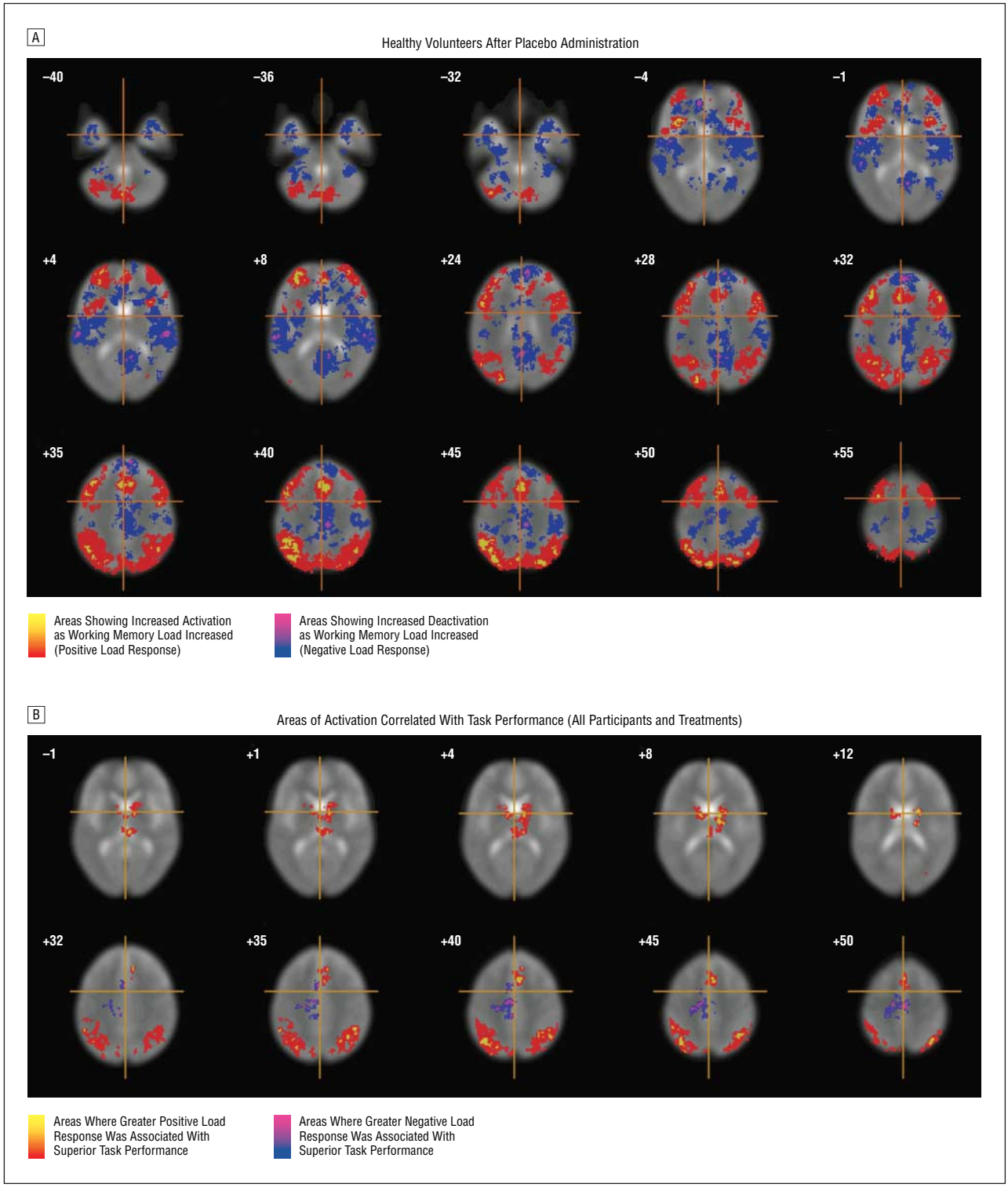

Figure 1. Maps of brain function during performance of the N-back working memory task. A, Systems of positive and negative brain load response in healthy volunteers after placebo administration (n=11), constituting a normal pattern of frontoparietal activation (red and yellow voxels) and temporocingulate deactivation (blue and purple voxels). B, Systems of significant psychophysiological association between behavioral performance, area under the task performance curve (AUC[Pr]), and positive or negative brain load response across all participants and treatments (n=66). The right side of each map represents the left side of the brain; the crosshairs indicate the origin of x and y dimensions, and the numbers denote the z dimension of each section in Talairach space.

treatments, performance was approximately 10% impaired in the schizophrenic patients. Within the healthy volunteer group, performance decrements were due to both lorazepam (–2.5% compared with placebo) and flumazenil (–3.1%). Within the patient group, the performance-degrading effect of lorazepam was more marked (–7.4%), and flumazenil had a performance-enhancing effect (+6.7%).

The ANOVA results, with drug treatment as a within-subject factor and diagnostic group as a between-subjects factor, showed a significant main effect of drug

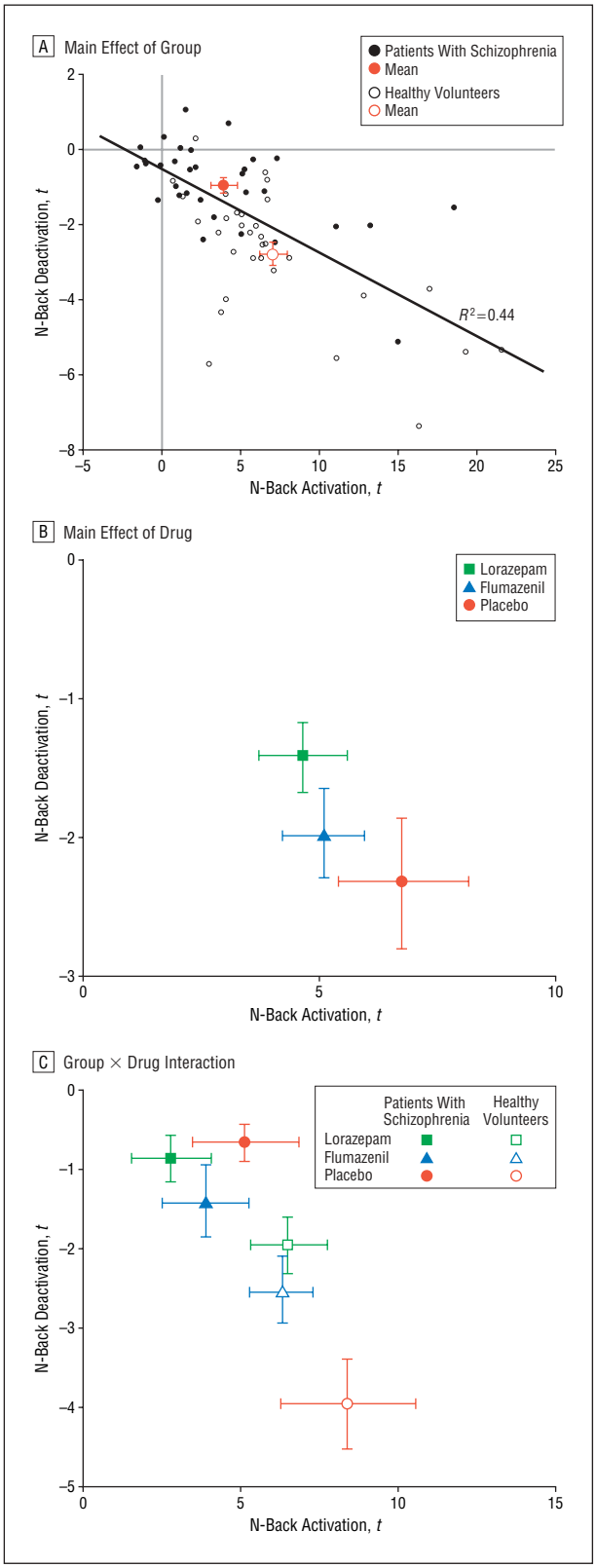

Figure 2. Effects of schizophrenia and γ-aminobutyric acid–modulating drugs on N-back activation and deactivation systems. A, Scatterplot of individual mean positive and negative load responses showing a strong correlation between the magnitude of frontoparietal activation and temporocingulate deactivation across all participants and reduced group mean activation and deactivation in patients with schizophrenia. B, Mean positive and negative load response (averaged across both groups after each treatment) showing strongest activation and deactivation after placebo administration. C, Mean positive and negative load responses (averaged for each group after each treatment) showing reduced activation and deactivation after lorazepam and flumazenil administration in healthy volunteers and enhanced deactivation in patients with schizophrenia after flumazenil administration. Error bars represent standard error of the mean; *t*, *t* statistic for the regional mean load-response.

Table 3. Behavioral Performance on a Verbal N-Back Paradigm as a Function of Working Memory Load, in Schizophrenic Patients and Healthy Volunteers After Administration of Placebo, Lorazepam, or Flumazenil

Drug	Working Memory Load	Behavioral Performance, Mean (SD)*	
		Healthy Volunteers (n = 11)	Schizophrenic Patients (n = 11)
Placebo	N = 0	0.91 (0.17)	0.82 (0.29)
	N = 1	0.85 (0.24)	0.68 (0.36)
	N = 2	0.79 (0.30)	0.61 (0.40)
	N = 3	0.79 (0.29)	0.50 (0.40)
	AUC(Pr)†	5.48 (0.39)	4.94 (0.87)
Lorazepam	N = 0	0.81 (0.31)	0.71 (0.50)
	N = 1	0.80 (0.29)	0.46 (0.53)
	N = 2	0.76 (0.35)	0.46 (0.49)
	N = 3	0.74 (0.35)	0.59 (0.49)
	AUC(Pr)†	5.34 (0.44)	4.57 (1.02)
Flumazenil	N = 0	0.89 (0.21)	0.88 (0.23)
	N = 1	0.79 (0.34)	0.77 (0.29)
	N = 2	0.73 (0.34)	0.75 (0.36)
	N = 3	0.67 (0.39)	0.63 (0.38)
	AUC(Pr)†	5.31 (0.54)	5.27 (0.55)

Abbreviation: AUC(Pr), area under the task performance curve.
*Calculated as a discrimination index (Pr) by subtracting the proportion of nontarget items incorrectly identified as targets (false alarms) from the proportion of items correctly identified as targets (hits).
†Total working memory performance AUC(Pr) was summarized by calculating the area under each subject's curve of the discrimination index (Pr) vs task difficulty.

($F_{2,40}$=4.25; P=.02) and a drug×group interaction ($F_{2,40}$=4.85; P=.01) on the AUC(Pr). Again, the drug×group interaction was due to an increased susceptibility of the patients to improved performance after flumazenil administration and impaired performance after lorazepam administration.

Response Latency

Results of the ANOVA of response latency showed a main effect of load ($F_{2.5,50.2}$=36.1; P<.001), with an expected increase in latency as task difficulty increased. In addition, we found a group×difficulty

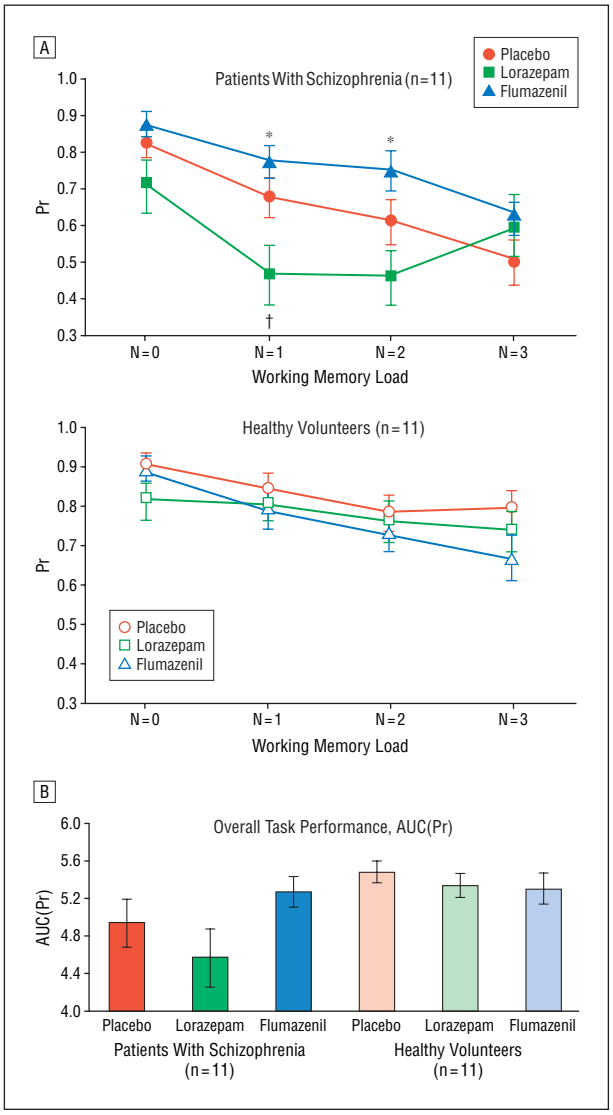

Figure 3. The N-back working memory task performance in patients with schizophrenia and healthy volunteers after treatment with flumazenil, lorazepam, or placebo. A, Drug effects on behavioral performance (Pr) as a function of task difficulty for patients with schizophrenia (top) and healthy volunteers (bottom). *Improved performance after flumazenil compared with placebo administration; at N=1, t_{43}=–2.14; P=.04; at N=2, t_{43}=–2.32; P=.03. †Worse performance after lorazepam compared with placebo administration (post hoc t_{43}=3.1; P=.003). B, Task performance accuracy summarized across all difficulty levels by the area under the task performance curve (AUC[Pr]). Error bars represent standard errors of means. Patients with schizophrenia showed a significant effect of drug on AUC(Pr) (post hoc analysis of variance [ANOVA] $F_{2,20}$=6.06; P=.009), but there was no significant effect of drug in healthy volunteers (post hoc ANOVA $F_{1.4,13.5}$=1.00; P=.36).

interaction ($F_{2.5,50.2}$=6.03; P=.002) because latency was not greatly prolonged by increased task difficulty in the patient group. There was no effect of drug or a group × drug interaction on latency, implying that nonspecific sedative or slowing effects of drug treatment were not prominent.

N-BACK ACTIVATION AND DEACTIVATION

To map brain areas normally activated or deactivated during the N-back working memory task, we first estimated the load response in fMRI data acquired only from healthy volunteers after placebo administration (Figure 1 and supplemental material [available at http://www-bmu.psychiatry.cam.ac.uk/data/menzies]). This demonstrated that a large-scale system of regions had a positive load response (increased activation as the task difficulty increased), including the cerebellum and the bilateral prefrontal and premotor (approximate Brodmann areas [BAs] 6, 8, 9, 10, 44, 45, 46, and 47), parietal (BAs 7 and 39), and anterior cingulate (BA 32) cortices. There was also a system of distributed regions with the opposite pattern of a negative load response (increased deactivation as the task difficulty increased), including the cerebellum, the bilateral temporal (BAs 20, 21, 28, 36, 38, 41, and 42), posterior cingulate and parietooccipital (BAs 2, 18, 19, 23, 24, 31, and 40), and medial frontal and anterior cingulate (BAs 6, 8, 9, 11, 24, 25, and 32) cortices, and the striatum. For the sake of brevity, we will subsequently describe these 2 complementary systems as the N-back activation and deactivation networks, respectively.

Considering the load-response statistics estimated in these regions for all participants, we found that the magnitude of activation and deactivation were significantly correlated (r=0.66; n=66; P<.001), that is, participants who showed the strongest positive load response in the N-back activation network tended to show the strongest negative load response in the N-back deactivation network (Figure 2A). The schizophrenic patients showed reduced activation and reduced deactivation compared with the healthy volunteers (Figure 2C) (ANOVA: main effect of group on activation and deactivation [as summarized by absolute sum of mean load-response statistics across both networks]; $F_{1,20}$=5.29; P=.03). On average across all subjects, lorazepam and flumazenil also tended to reduce activation and deactivation (Figure 2B). (ANOVA: main effect of drug on activation and deactivation; $F_{1.49,29.7}$=3.63; P=.05.) However, consideration of drug effects separately by group showed that, whereas both GABA-modulating drugs reduced activation and deactivation in healthy volunteers and lorazepam also reduced activation in schizophrenic patients, flumazenil tended to enhance deactivation in the patient group (Figure 2C). (ANOVA: group × drug interaction on deactivation; $F_{1.68,33.5}$=8.93; P=.001.) A finer-grained localization of regions in the N-back activation and deactivation networks showing group and drug effects is provided by additional maps and tables in the supplemental material (available at http://www-bmu.psychiatry.cam.ac.uk/data/menzies).

NEUROPHYSIOLOGICAL CORRELATES OF TASK PERFORMANCE

The extent of activation and deactivation (as summarized by the absolute sum of the mean load-response statistics across the 2 networks) was correlated with behavioral performance as summarized by the AUC(Pr) (r=0.48; n=66; P<.001). This indicates that participants who performed the task better tended to activate the frontoparietal cortex and deactivate the temporocingulate cortex more strongly than did those with poor task performance.

To specifically address the relationship between task performance and brain function, we performed a second analysis in which we regressed the summary performance measure AUC(Pr) on the load response at each voxel of fMRI data. We found 2 main classes of brain regions where variable task performance significantly predicted physiological load response (Figure 1B and supplemental material [available at http:www-bmu.psychiatry.cam.ac.uk/data/menzies]). Superior task performance predicted a greater positive load response in the anterior cingulate and medial frontal cortex (BAs 24 and 32), the bilateral posterior parietal cortex (BAs 7, 39, and 40), the thalamus, and the caudate nucleus. In these areas, better-performing individuals showed increased brain activation with increasing task difficulty. In addition, superior task performance predicted a greater negative load response in the posterior and dorsal cingulate cortices (BAs 23 and 24). In these areas, better-performing individuals showed decreased deactivation with increasing task difficulty. These opposing changes in activation as a function of increased task difficulty were associated across all subjects (mixed-effects regression, $t_{43}=-7.29$; $P<.001$), meaning that the subjects who performed well had marked increases in frontoparietal activation and marked decreases in posterior cingulate activation at difficult levels of the task (**Figure 4**).

Exploratory plots of the AUC(Pr) vs load response in each of these regions considered separately (**Figure 5**) confirmed that (1) schizophrenic patients generally performed poorly and had a reduced positive or negative load response compared with healthy volunteers; (2) the effect of lorazepam markedly reduced the load response in schizophrenic patients; and (3) improved performance by schizophrenic patients after flumazenil administration was associated with an increased positive load response in the anterior cingulate cortex.

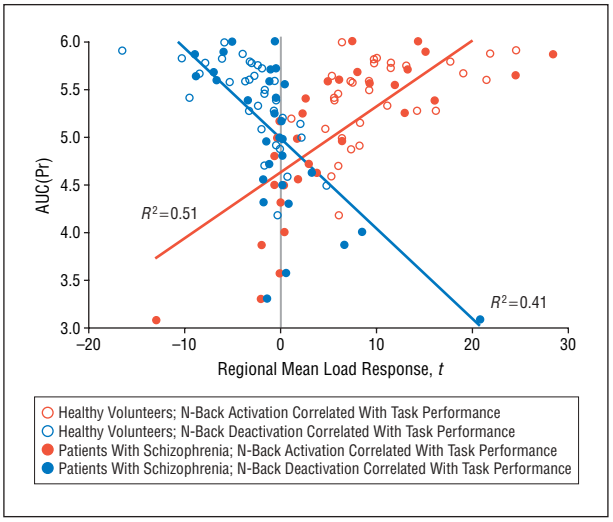

Figure 4. Physiological correlates of working memory task performance in patients with schizophrenia and healthy volunteers after administration of lorazepam, flumazenil, or placebo. Scatterplot of the area under the task performance curve (AUC[Pr]) vs positive and negative load responses averaged across all voxels in the systems shows significant association with task performance for all participants and treatments (n=66). Superior performance is associated with greater frontoparietal activation and greater dorsal cingulate deactivation.

COMMENT

The 2 main hypotheses under investigation in this study were both substantiated by the data. We found that the GABA-modulating drugs had differential effects on behavioral measures of working memory performance in schizophrenic patients compared with healthy volunteers. We also found that variation in cognitive performance was generally correlated with variation in brain function and that schizophrenic patients demonstrated an abnormal pattern of drug effects on frontoparietal activation and temporocingulate deactivation.

BEHAVIORAL EFFECTS OF GABA-MODULATING DRUGS ON TASK PERFORMANCE

After placebo administration, the schizophrenic patients had a relatively impaired working memory performance compared with healthy volunteers. As shown in Figure 3 and Table 3, lorazepam impaired performance in all participants, but the degree of impairment was greater in the patient group. The effects of flumazenil were also different between groups: a tendency for impaired performance in healthy volunteers contrasted with a significant enhancement of performance in schizophrenia patients (for post-hoc *t* tests, see Figure 3). These observations cannot be explained readily in terms of differential drug effects on processing speed or general sedative drug effects (eg, lorazepam) because there was no significant group × drug interaction for response latency. However, they are compatible with the hypothesis that cognitive deficits in schizophrenia are related to inhibitory neuronal abnormalities.

There is now considerable histopathological evidence indicating cellular abnormalities of inhibitory interneurons in schizophrenic patients.[11,12,26] The parvalbumin-expressing, chandelier class of cortical interneurons is most clearly implicated in the pathophysiology of schizophrenia.[30,59] These cells, concentrated in neocortex layers III through V, form clustered inhibitory synapses on axon initial segments and somas of pyramidal cells and are thus powerfully positioned to coordinate pyramidal firing. Cellular abnormalities of GABA interneurons have been reported, especially in the anterior cingulate and prefrontal cortices, in postmortem studies of schizophrenia.[27,28,60] There is also evidence of reduced prefrontal expression of messenger RNA coding the GABA-synthesizing enzyme glutamic acid decarboxylase and the trophic protein reelin, which is released presynaptically from some classes of interneurons and is involved in sustaining the plasticity of dendritic spines on pyramidal cells.[30,31,61-65]

These presynaptic changes would be expected to attenuate inhibitory neurotransmission by cortical interneurons. However, there is also evidence of reduced prefrontal expression of messenger RNA coding the GABA membrane transporter 1,[46] which would tend to increase synaptic availability of GABA, and increased postsynaptic density of $GABA_A$ receptors,[27-29] which would tend to enhance postsynaptic inhibitory GABA effects. It has been persuasively argued that the primary patho-

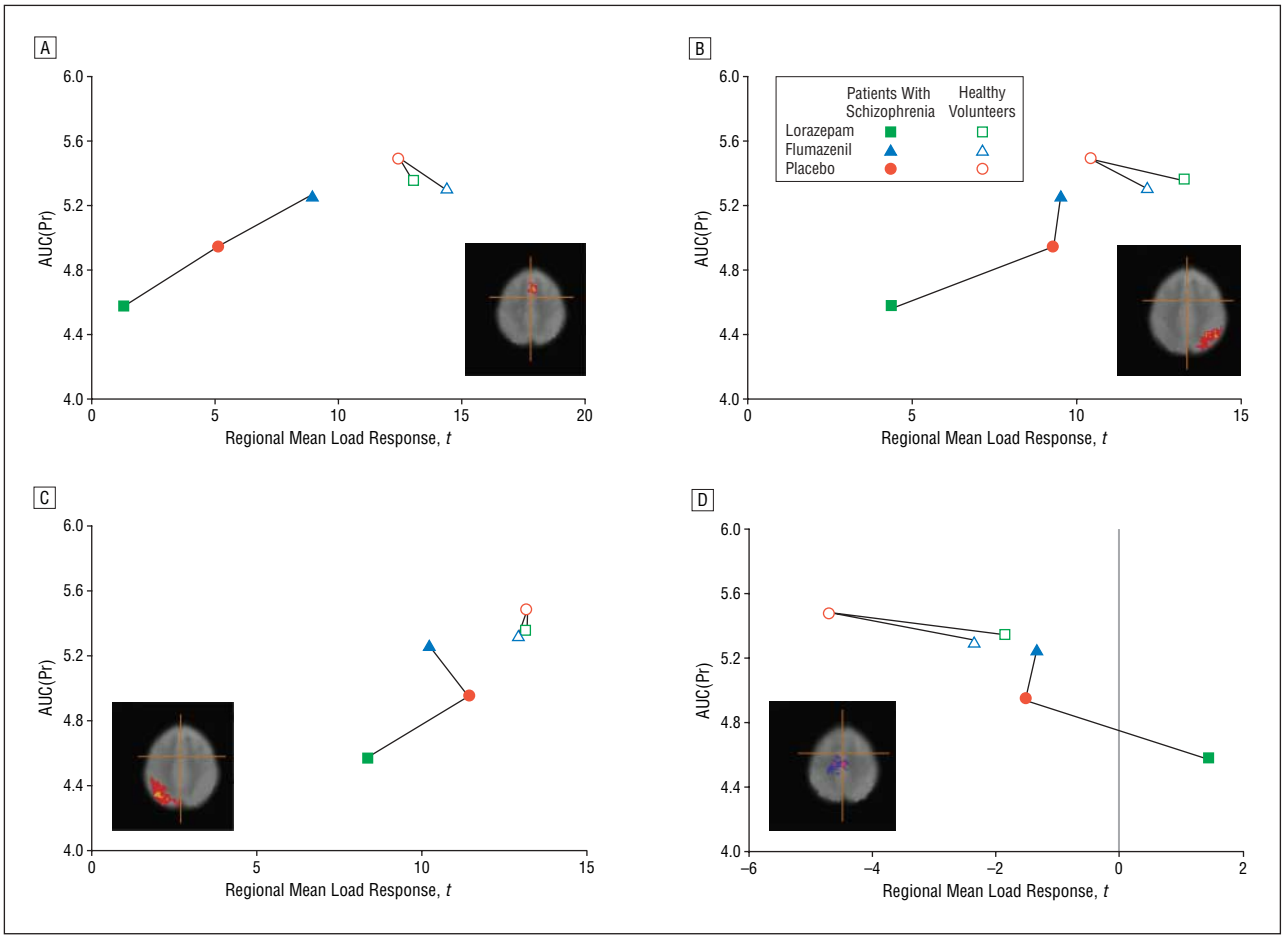

Figure 5. Effects of schizophrenia and γ-aminobutyric acid–modulating drugs on positive and negative load response in brain regions significantly associated with behavioral task performance. Plots of the mean area under the task performance curve (AUC[Pr]) vs regional mean load response are shown separately by group and drug for 4 representative regions of significant psychophysiological association. A, Anterior cingulate cortex shows increased activation associated with superior performance in patients with schizophrenia after flumazenil administration. B and C, Bilateral parietal cortex shows attenuated activation associated with worse performance in patients with schizophrenia after lorazepam administration. D, Dorsal cingulate cortex shows attenuated deactivation after administration of both drugs in healthy volunteers and after lorazepam administration in patients with schizophrenia.

genetic event is presynaptic down-regulation of GABA synthesis, which triggers compensatory changes in postsynaptic receptor density.[11,12,32] However, it is currently unclear whether the net effect of presynaptic down-regulation of GABA synthesis and release, combined with postsynaptic compensatory changes in $GABA_A$ receptor density, is to increase or to decrease the inhibitory tone prevailing on pyramidal cells.

Our behavioral data, indicating that working memory deficits in schizophrenia can be exacerbated by lorazepam (a positive allosteric modulator of GABA transmission) and ameliorated by flumazenil (an antagonist or a partial inverse agonist at the $GABA_A$ receptor), are compatible with the view that cognitive impairment may reflect a pathological state of overinhibition in schizophrenia. These data imply that postsynaptic changes supposed to compensate for presynaptic down-regulation of GABA synthesis must in some sense be overcompensatory.

N-BACK ACTIVATION AND DEACTIVATION NETWORKS

In healthy volunteers undergoing MRI after placebo administration, the performance of the N-back working memory task at increasing levels of difficulty predictably engendered increasing activation in a large-scale system consisting of the prefrontal, premotor, anterior cingulate, and parietal cortices and the cerebellum. A similar activation pattern was reported in a meta-analysis of 24 functional neuroimaging studies of the N-back paradigm,[38] and positive load-response properties of the prefrontal, premotor, and anterior cingulate cortices have been reported across a diverse range of cognitive tasks.[66]

In addition, we found in healthy volunteers after placebo administration that increasing task difficulty caused increasing deactivation in a large-scale system consisting of the lateral temporal, dorsal, and posterior cingulate cortices. Deactivation of similar regions has previously been reported in some working memory studies; posterior cingulate deactivation, in particular, has been reported across a wide range of cognitive tasks.[67-71] Theoretical interest in fMRI deactivation has focused recently on the idea that common patterns of deactivation across multiple experimental tasks may represent reallocation of activation resource from a resting or "default mode" network, including the posterior cingulate cortex, to other brain regions specialized for processing task demands.[72-75] More generally, we can think of the brain

as more or less efficient in rationing a finite activation resource between functionally competitive large-scale neurocognitive systems.[70,72,73,76] In keeping with this economic model, it has been shown previously, as well as in these data, that a greater magnitude of activation in task-related regions is associated with a greater magnitude of deactivation in default regions.[70,76] We have further shown, for the first time, that the strength of correlated activation/deactivation—or efficiency of competition—between task-related and default systems is associated with superior cognitive performance.

In this theoretical context, we interpret the fMRI data in schizophrenic patients as indicating relative inefficiency of resource reallocation between competitive systems. Similar patterns of reduced frontal activation and/or reduced lateral temporal deactivation have been reported in functional neuroimaging studies of schizophrenia and discussed in terms of hypofrontality or frontotemporal dysconnectivity.[77-81] Neurocognitive inefficiency has also been invoked conceptually to describe abnormal associations between cognitive performance and the magnitude of frontal activation in schizophrenia.[82,83] However, neurotransmitter mechanisms for these functional neuroimaging phenomena have not previously been investigated.

On the basis of our observation that lorazepam and flumazenil reduced both frontoparietal activation and temporocingulate deactivation in healthy volunteers, we suggest that normal inhibitory interneuronal function is critical for efficient systems competition.

The more salient effects of lorazepam on brain function in schizophrenic patients, which were essentially to exaggerate the disease-related profile of competitive inefficiency, suggest that abnormalities of GABA neurons may also subtend abnormalities of large-scale correlated brain activation in schizophrenia.

THERAPEUTIC IMPLICATIONS

The main clinical inference from these data is that cognitive adverse effects of benzodiazepines should be monitored closely in schizophrenia. Few studies have examined the effects of benzodiazepine on cognition in schizophrenia, with the exception of a single photon emission tomography study suggesting a differential relationship between benzodiazepine receptor binding and cognitive performance in schizophrenic patients compared with healthy controls.[84] Our data indicate that a single dose of lorazepam administered to schizophrenic patients can cause deterioration of working memory to a much greater extent than the same dose administered to healthy controls.

Few published reports have examined pharmacotherapies for cognition in schizophrenia. These include discussion of the benefits of atypical vs typical antipsychotics[85,86] and, motivated by the cholinergic model of Alzheimer disease, an interest in cholinergic agonists and acetylcholinesterase inhibitors.[87] Most recently, Spence et al[88] reported increased activation of the anterior cingulate, correlated with N-back performance, in schizophrenic patients after modafinil administration. Based on data indicating a primary presynaptic deficit in GABA synthesis, there is interest in the use of α_2-selective $GABA_A$ agonists,[12,32] but there are no empirical data yet available to support this. Our results alternatively suggest that further efforts to discover GABA-modulating drugs for cognition might justifiably include compounds with inverse agonist or antagonist properties at the benzodiazepine site, like flumazenil but more conveniently administered.

METHODOLOGICAL ISSUES

Our sample size is small and there are attendant risks of type II (false-negative) error. The schizophrenic patients were receiving medication and were chronically ill (Table 2). It is difficult to predict the interactions that may occur between antipsychotics and the GABA-modulating drugs used herein, and thus it is unclear how generalizable these results would be to first-episode or medication-naive patients (although Perault et al[89] report a lack of interaction between the effects of lorazepam and an atypical antipsychotic on memory). In addition, we assumed a linear relationship between task difficulty and physiological load response; this may be a simplistic assumption necessitated by the limited number of levels of task difficulty available for modeling nonlinear load response.[82] Pharmacological MRI is increasingly used for measuring the functional effects of psychoactive drugs on large-scale neurocognitive systems.[90] However, interpretation of pharmacological MRI findings is complex. It is possible that GABA-modulating drugs could cause changes in task-related blood oxygen level–dependent contrast by direct vascular effects, although the correlation between fMRI findings and behavioral outcome measures reduces the plausibility of this interpretation of our findings.

CONCLUSIONS

We have reported evidence of differential effects of GABA-modulating drugs on cognition and related brain function in schizophrenic patients compared with healthy volunteers. We argue that these results are compatible with a pathological state of overinhibition in schizophrenia, leading to inefficient reallocation of activation resources between task-related and default brain systems.

Submitted for Publication: October 21, 2005; final revision received April 21, 2006; accepted May 2, 2006.
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Author Contributions: Ms Menzies and Dr Ooi contributed equally to this work. Dr Bullmore was the principal investigator, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: None reported.
Funding/Support: This study was supported by the Wellcome Trust (Dr Bullmore); by a Margaret Temple Fel-

lowship from the British Medical Association (Dr Stephenson); and by the Harnett Fund from the University of Cambridge (Ms Menzies). Software development was supported by a Human Brain Project grant from the National Institute of Biomedical Imaging and Bioengineering and the National Institute of Mental Health. The Wolfson Brain Imaging Centre is supported by the Medical Research Council of the United Kingdom.

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