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Functional Neuroanatomy of Sustained Attention in Schizophrenia: Contribution of Parietal Cortices

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Abstract: Deficits in sustained attention have been frequently described in schizophrenia. The neuroanatomical basis reported previously have included altered levels of activation in cingulate and prefrontal cortex, but the contribution of further regions remains unclear. We explored the full neuroanatomy underlying the sustained attentional deficits observed in naïve schizophrenics compared with controls. Participants included 10 controls and 11 patients. The experimental design included rest, auditory stimulation using clicks, and two counting tasks. Subjects were instructed to mentally count the clicks, and then to count forward at the same frequency they heard previously when listening to the clicks. Relative cerebral blood flow (relCBF) was measured by means of PET ^{15}O-water. Differences were observed between both groups at superior temporal cortex, superior parietal gyrus, and cerebellum during tasks requiring listening. During all counting conditions, additionally to supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPCF), precentral gyrus, cingulate, cerebellum, and inferior parietal (IP) gyrus, patients engaged other frontal structures including inferior, medial, and superior frontal areas. When counting with no auditory stimulation (C; requires components of working memory and time estimation), significant differences were observed in the level of activation of frontal and IP regions. Our naïve patients presented abnormal activation of auditory associative pathways. They failed to activate prefrontal and parietal regions at a similar level during tasks requiring increased cognitive effort, and they required a higher activation of inferior frontal regions to properly respond to cognitive demands. *Hum. Brain Mapping 17:116–130, 2002.*

Key words: schizophrenia; counting; auditory processing; attention; PET; working memory; time estimation; parietal lobes

INTRODUCTION

Deficits in attention have been considered essential to schizophrenia since Bleuer [1911] and Kraepelin [1913]. Further contributions have been made to consider attentional difficulties as a key symptom and an underlying mechanism to more complex cognitive deficits in schizophrenia [Levin et al., 1989]. Deficient performance in attentional tasks is a stable, long-lasting characteristic of the disorder identified either during acute or chronic states, and independent of neu-

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roleptic medication. The exact course and biological bases of these deficiencies, however, remains obscure. An increased interest in the relationship between attentional deficits and vulnerability to schizophrenia has been reported [Asarnow et al., 1978; Braff et al., 1982; Nuechterlein et al., 1984]. Current international classification systems for the diagnosis of schizophrenia do not include specific criteria related to these deficiencies. Structured tools and scales utilized for the clinical evaluation of the severity of the symptoms (i.e., SAPS/SANS, BPRS, PANSS) include items to measure attention.

Sustained attention is most often studied in schizophrenia and requires subjects to minimize distractibility, maintain alertness, and focus attention on stimuli within a sensorial modality. The main interest in sustained attention deficits in patients with schizophrenia is its persistence regardless of treatment. Contrary to other symptoms that clearly seem to improve with medication, sustained attention problems seem to be unchanged after treatment [Sax et al., 1998], suggesting that they could be used as trait marker for the illness [Maruff et al., 1999].

Contemporary conceptualization of cognitive deficits in schizophrenia studies tends to place less emphasis on attentional difficulties as being synonymous of prefrontal cortex dysfunction, while maintaining a focus on the frontal-subcortical circuits believed to subserve many of these functions [Goldman-Rakic, 1991; Jones, 1997; Palmer et al., 2000]. As pointed out by Weinberger et al. [1996], although some aspects of schizophrenia clearly relate to frontal dysfunction, this disorder does not seem to be explainable exclusively by a simple model of focal frontal vulnerability.

Neuroimaging researches have employed standard neuropsychological tests of combined stimulation, mainly Continuous Performance Test (CPT) [Buchsbaum et al., 1990; Cohen et al., 1988], to study the anatomofunctional bases of sustained attention in both normal subjects and patients with schizophrenia.

Specific prefrontal regions and cingular gyrus seem to be involved in tasks requiring attention, as well as in monitoring cognitive effort during working memory and other mental processes [Grady et al., 1997; Halpern et al., 1999; Petrides et al., 1993; Zatorre et al., 1994]. The activation observed in these regions seems to be connected not to the particular sensory modality of the stimuli, but to underlying aspects of the task requirements.

The contribution of studies employing PET ^{15}O-water for assessment of cerebral blood flow is relevant in the clarification of the specific role of brain regions during cognitive performance, especially during attentional tasks. Table I shows a summary of published studies using PET ^{15}O-water during various cognitive demands in schizophrenia, including attention.

TABLE I. PET-$H_2{}^{15}O$ studies in basal state and cognitive activation tasks in schizophrenia

Condition	Study
Basal state	Early et al., 1987 Silversweig et al., 1995 Miller et al., 1997 Andreasen et al., 1997 Epstein et al., 1999 Kim et al., 2000
Activation	
Attention	O'Leary et al., 1996 Carter et al., 1997 Holcomb et al., 2000
Verbal fluency	Fletcher et al., 1996 Friston et al., 1996 Dye et al., 1999 Artiges et al., 2000 Spence et al., 2000 Josin et al., 2001
Memory	Andreasen et al., 1996 Ganguli et al., 1997 Wiser et al., 1998 Ragland et al., 1998 Carter et al., 1998 Fletcher et al., 1999 Artiges et al., 2000 Bertolino et al., 2000 Crespo-Facorro et al., 2001
Executive function	Ragland et al., 1998

Further research will help clarify the specific role of the cingulate region during auditory attention and the additional participation of other brain structures connected with the cingulate or engaged during the same cognitive activities. Neuroimaging studies are consistent overall with the historical interest in the potential role of abnormalities in frontal or frontal-subcortical circuitry in the genesis of schizophrenia [Palmer et al., 2000]. In this framework we are faced with several questions, including (1) how neuroanatomical bases help to explain attentional deficits; (2) how attentional deficits impact the everyday functioning of patients; and (3) how to develop effective interventions, present or potential, for attentional deficits.

We investigated the underlying neural networks of auditory sustained attention with PET-water in schizophrenic patients and comparison subjects. We have chosen a single paradigm based on counting

TABLE II. Subjects performance mentally counting the clicks

	Counting while listening			Counting without listening		
	Actual clicks	Subject's report	Difference	Seconds/Clicks	Subject's report	Difference
Controls	132.7 ± 35.3	133.6 ± 35.3	−0.9 ± 3.5	117.8 ± 7.2	105.4 ± 27.9	12.3 ± 31
Patients	122.8 ± 14.6	119.7 ± 35.8	3.1 ± 8.4	121.6 ± 8.6	107.6 ± 14.1	14 ± 3.4

* Values are expressed as mean ± SD.

auditory stimuli and counting mentally without external stimulation, to assess the neuroanatomical structures involved in sustained attention and working memory aspects.

SUBJECTS AND METHODS

Subjects

The study was approved by the University-Hospital Clinic of Navarra Ethics Committee Review Board. All subjects gave written informed consent after the procedure was explained fully to them. Eleven patients and 10 normal healthy controls participated. All subjects were right-handed as determined by the Anett Questionnaire [Anett, 1967] and were in good physical health. Normal auditory capacity of the subjects was evaluated as part of their medical screening to confirm perfect hearing. Candidates with a history of substance abuse, neurological conditions, head trauma with loss of consciousness, diabetes, hypertension and asthma were excluded from the study.

Schizophrenics and controls were matched on age (mean age for patients = 27.55, SD = 9.4; controls = 26.10, SD = 6.95), gender (male/female rate for patients = 10/1; controls = 7/3), and years of formal education (mean years for patients = 12.93 ± 1.90; controls = 14.67 ± 2.71). No differences in estimated IQ (as measured by the Barona Index) were observed between groups.

All patients met DSM-IV criteria for schizophrenia. Eight schizophrenics were fully naïve, and three patients took medication with a required minimum wash-out period of 1 month before the study (mean wash-out period = 3 months). Mean age of illness onset was 17.73 years (SD = 4.7) with a mean duration of 10 years of illness (X = 9.82, SD = 7.8) from first diagnosis to date of study. Schizophrenic symptoms were classified as positive or negative using PANNS Scale [Kay et al., 1987]. Seven patients were classified with positive symptoms and four patients were classified with negative symptoms.

Procedures

There were four task conditions used in this study: (1) auditory stimulation (Task A); (2) counting task with auditory stimulation (Task A+C); (3) counting task with no auditory stimulation (Task C); and (4) a rest condition. Auditory stimulation was carried out using an earphone. Stimulation included a series of non-filtered clicks, applied binaurally, at 90-dB intensity and 1-Hz frequency. An auditory click stimulator (S10CTCM; Grass, West Warwick, RI) was used to generate the clicks.

Task A

Subjects were exposed to repeated auditory clicks provided at a predetermined, consistent rate (1/second).

Task A+C

In addition to the previous condition, subjects were asked to mentally count the number of clicks to which they were exposed. A sustained attention and working memory demand was implied. The rate of serial counting is regulated because of the need to attend to an external auditory stimulus.

Task C

Subjects were asked to mentally count at the same rate at which the clicks were presented in previous conditions. This time no auditory stimulation was provided. During the conditions of counting with and without auditory stimulation, subjects were encouraged to avoid finger and oral movements to facilitate the counting tasks. The ability of a subject to count properly was controlled by an external examiner who asked for and registered the total number of clicks recalled by the subject at the end of each counting condition. Table II shows the results reported by controls and patients for both conditions. Differences be-

tween groups were not found to be statistically significant for the Task A+C condition ($t = 0.42$, $P = 0.68$) or for the Task C condition ($t = -0.59$, $P = 0.56$).

Rest condition

Subjects lay quietly and residual background noise was kept to a minimum. They kept their eyes open and their gaze was fixed on the ceiling of a dimly lit room. No specific instructions about mental activity were provided in this condition.

PET scan

Each subject was scanned four times in a single PET session, measuring relative cerebral blood flow (relCBF) by means of ^{15}O-water with standard laboratory procedures.

The scans were performed with an ECAT EXAT HR+ (Siemens/CTI, Knoxville, TN) that collects 63 parallel planes over a 15.2-cm axial field of view. During all conditions patients were tied and an external observer guaranteed no visually significant movements. To minimize the head movement, a head belt was fastened to the head holder. Transmission scanning was done prior to radiopharmaceutical injection using three rotating rod sources of ^{68}Ge.

Measurements of relCBF were made after an i.v. bolus injection of 10 mCi of $H_2{}^{15}O$-water in 5–7 ml of saline. Scans were initiated automatically when the radioactive count rate in the brain reached a threshold value of 100 Kcounts per second, approximately 20 seconds after i.v. injection, and continued for 60 seconds. Data were acquired and reconstructed in full 3D mode (e.g., septa retracted).

The PET images from each subject were centered (left–right), vertically aligned to correct for movement in the transverse and coronal planes, and co-registered one to another, to correct for slight head movement during the scan (AIR) [Woods et al., 1992]. All other PET scans collected for one subject were then mathematically registered to the first scan by PET–PET alignment (AIR). These processes centered the images and oriented them in the same coordinate system for later processing.

Data analysis

Statistical analysis of the data was carried out using the Statistical Parametric Mapping program (SPM99) [Friston et al., 1991] in MATLAB (Mathworks, Sherborn, MA). The scans were spatially normalized using linear transformation, which removed individual subject variability and transformed each brain into the Talairach and Tournoux atlas reference space [Talairach et al., 1988]. The scans were then smoothed at 12 mm with a 3D Gaussian filter to suppress noise and minimize effects of normalization errors by increasing the sensitivity of the signal.

Differences in global activity within and between subjects were removed by proportional scaling on a voxel-by-voxel basis with global counts as covariate and regional activity across subjects for each task as treatment effect. Proportional scaling was used for the comparison of tasks, with each subject being studied in all conditions. Inter-subject variability was treated as a random effect to avoid false positives. Comparisons of the means across selected conditions were made on a voxel-by-voxel basis using the t test. The resulting values constituted a statistical parametric map (SPM). The critical level of α was set at 0.001 (uncorrected for multiple comparisons).

SPM analysis of subtractions was carried out for all subjects using a standard subtractive methodology utilized previously in studies of functional neuroimaging and cognition [Petersen et al., 1989; Tracy et al., 2000]. In this methodology, experimental conditions are compared directly. This strategy was chosen because comparisons at rest are difficult to interpret, and activation attributed to Task A+C and Task C conditions needed to exceed the activation in the control conditions (including the Task A condition), regardless of the presence of activation in these conditions compared to a resting baseline. In the case of the Task C condition, subjects were required to count mentally at the rate of clicks they had listened to previously, in the Task A and Task A+C conditions. The activation related to this component should present differences compared to the activation observed during Task A and Task A+C.

RESULTS

Cognitive data

All subjects went through a battery of cognitive tests to examine their neuropsychological performance in terms of attention, working memory, verbal fluency, and executive functions. The selection of these cognitive abilities was based on their participation in the experimental conditions. The measures included the Continuous Performance Test (CPT), the Brief Test of Attention (BTA), Digits (WAIS-III), Trail Making Test Parts A & B (TMT), FAS, and Wisconsin Card Sorting Test (WCST). As shown in Table III, the general performance of the patients was significantly worse than

TABLE III. Summary of cognitive performance and differences between normal controls and naïve patients with schizophrenia

Cognitive function	Neuropsychological test	Mean performance ± SE		Significance
		Controls (n = 10)	Patients (n = 11)	
Attention	CPT (reaction time)	420.81 ± 65.4	428.75 ± 84.4	0.821
	CPT (global index)	3.711 ± 4.3	4.17 ± 5.5	0.841
	BTA (total)	18.4 ± 1.26	15.1 ± 3.93	0.021*
	Digits (total), WAIS	20.1 ± 5	16.10 ± 4.7	0.082
	Trail Making Test A (seconds)	27.8 ± 8.93	48.9 ± 15.7	0.002*
	Trail Making Test A (errors)	0.0 ± 0.0	0.0 ± 0.0	1.000
	Trail Making Test B (seconds)	52.10 ± 12.25	111.9 ± 35	0.000*
	Trail Making Test B (errors)	0.1 ± 0.32	0.7 ± 1.1	0.103
Verbal fluency	FAS (total letters)	50.20 ± 9.93	32.10 ± 10.08	0.001*
	FAS (animals)	26.9 ± 3.63	17.70 ± 5.62	0.000*
	FAS (supermarket)	25 ± 6.13	16.20 ± 3.91	0.001*
Executive functions	WCST (categories completed)	5.5 ± 0.76	4.22 ± 2.22	0.144
	WCST (perseverative responses)	9.25 ± 6.73	24.11 ± 14.4	0.018*
	WCST (perseverative errors)	8.8 ± 6.33	20.33 ± 11.48	0.025*
	WCST (conceptual responses)	60.22 ± 14.2	61.9 ± 5.7	0.104
	WCST (conceptual responses)	60.22 ± 14.2	61.9 ± 5.7	0.104

* $P < 0.05$.

controls for measures of visual attention (TMT A), shifting, divided attention, working memory (measured by TMTB and BTA), verbal fluency (in letters and categories), and in the number of perseverative errors and responses in the WCST.

Task performance

To control the counting accuracy of subjects, at the end of the counting conditions they were asked to report the exact number of auditory stimuli that they had listened to. The examiner controlled the time of exposition and number of stimuli presented using a chronometer (mean range, 90–130 stimuli). Healthy controls and patients did not obtain significantly different performances ($P = 0.680$) in Task A+C compared to actual number of clicks presented (controls: mean = −0.88, SD = 3.5; patients: mean = 3.10, SD = 26.4), or in Task C (controls: mean = 20.29, SD = 19.25; patients: mean = 12.33, SD = 31.01, $P = 0.563$).

PET data

Auditory stimulation vs. no auditory stimulation

Activation relative to auditory stimulation (Task A) was measured by a comparison between the experimental conditions including auditory stimulation (Tasks A and A+C) and conditions with no auditory stimulation (Task C and rest). This comparison was made for both patient and control groups. Subtraction was intended to capture all the processes involved in listening to controlled external stimuli. Significant activation was observed in the transverse temporal convolutions (higher in the left hemisphere) including both medial temporal auditory cortex (BA 41), and posterior cingulate (BA 23) for both patients and normal controls independently. Normal controls increasingly activated other cortical association areas, such as the superior temporal cortex (BA 22), left superior parietal gyrus, and right cerebellum. In patients, the pattern of significantly increased brain activity included left middle frontal gyrus (BA 8) and left anterior cingulate (BA 32). When explicit comparison between groups was performed, significant differences in activation were found (increased changes for normal controls) at the level of inferior temporal gyrus ($Z = 3.26$), middle occipital gyrus ($Z = 3.18$), and parahippocampal gyrus ($Z = 3.11$). See Table IV for specific Z values and BA areas.

Counting vs. no counting

For the analysis of the activation related to counting, the non-counting tasks (rest and Task A) were used as control condition for the counting tasks (Task A+C and Task C). When this contrast was performed for

TABLE IV. Brain regions associated with significant relCBF changes related to main effect of listening the clicks in controls, patients, and controls minus patients

	Controls				Patients				Controls minus patients			
Region	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score
Frontal												
Medial frontal cortex					L	8	−32, 10, 26	3.06				
Posterior cingulate	R	31	8, −46, 40	3.8	R	23	6, −24, 22	2.88				
Anterior cingulate					L	32	−6, 8, 44	3.15				
Temporal												
Transversal temporal gyrus	L	41	−38, −28, 12	4.26*	L	41	−50, −20, 12	3.63				
	R	41	36, −20, 0	3.58	L	41	−28, −32, 18	3.02				
Superior temporal gyrus	L	22	−58, −42, 12	4.0								
	L	36	−26, 0, −32	3.34								
	R	22	60, −20, 8	3.47								
Middle temporal gyrus	R	21	70, −40, 4	3.58*	R	21	50, −8, −14	3.21				
Inferior temporal gyrus					R	20	30, −14, −46	2.77	R	20	−34, −10, −42	3.26
					R	20	22, −6, −48	2.7	R	20	−44, −10, −22	2.98
Parahipocampical gyrus									R	28	16, −16, −20	3.11
									R	28	14, −26, −18	2.97
Parietal												
Superior parietal gyrus	R	7	26, −54, 72	3.72								
Cerebelum	L		−26, −84, −36	3.18								
Medial occipital gyrus									L	19	−42, −74, 0	3.18

* Regions for which the level of activation was also significant at $P \leq 0.001$, corrected for multiple comparisons.

each group independently, significant increases of relCBF were observed in SMA, precentral gyrus, bilateral DLPF, cerebellum, anterior cingulate, and inferior parietal, for both normal and schizophrenic participants. When intergroup differences were statistically tested, data showed significant increased activation in normal subjects for cerebellum ($Z = 4.04$), SMA ($Z = 3.94$), and precentral gyrus ($Z = 3.85$). Additionally, patients showed significantly greater activation in bilateral inferior and middle part of the superior frontal gyrus, right middle temporal, and left middle frontal. Activation on right putamen and left inferior temporal gyrus at this condition was only seen for controls and not for patients. Specific values (Z scores) for all brain regions with significant changes in relCBF, their coordinates in standard stereotaxic space, and the corresponding Brodmann areas are displayed in Table V.

Counting without auditory stimulation vs. rest

To analyze activation in regions of interest during Task C, this condition was first compared to rest. As for controls, activation for patients with schizophrenia engaged the bilateral dorsolateral prefrontal cortex (DLPFC), left cerebellum, left inferior frontal, and right SMA. No activation was observed on the anterior cingulate or in precentral gyrus for patients, but these regions were significantly activated in controls for this condition. The patient group increasingly engaged bilateral middle temporal gyrus and supramarginal gyrus. When intergroup levels of activation were statistically compared, significant differences were observed at the level of right precentral gyrus ($Z = 5.28$), bilateral SMA ($Z = 3.60$) and right DLPFC ($Z = 3.60$; see Table VI).

Counting without auditory stimulation vs. counting with auditory stimulation

During Task C relative to Task A+C (counting with auditory stimulation) comparison subjects showed greater relCBF than patients in DLPFC, inferior parietal, cingulate, and SMA. Both groups engaged the precentral gyrus (right hemisphere for controls and

TABLE V. Brain regions associated with significant relCBF changes related to main effect of counting the clicks in controls, patients, and controls minus patients

	Controls				Patients				Controls minus patients			
Region	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score
Frontal												
Precentral gyrus	R	4	50, −8, 38	5.13*					R	4	52, −6, 38	3.85
	R	4	60, 6, 18	4.62*								
	L	6	−62, 2, 20	4.40*	L	6	−48, 4, 12	3.44				
Motor supplementary area	L	6	−8, 6, 62	4.40*	L	6	−2, 16, 60	4.41*	L	6	−10, −22, 68	3.94
	R	6	6, −2, 68	4.27*					R	6	6, −12, 68	3.51
Inferior frontal gyrus					R	47	54, 40, −12	5.31*				
					R	44–45	54, 14, 8	5.11*				
					L	45	−26, 20, 0	4.23				
Anterior cingulate	L	32	−12, 14, 46	4.06*	R	32	6, 32, 30	4.43*				
Dorsolateral prefrontal gyrus	R	9	30, 48, 20	4.18	R	10	38, 54, 2	5.29*				
	L	9	−36, 50, 26	3.74	L	10	−22, 52, −8	4.32				
Medial frontal gyrus					L	6	−46, 6, 50	3.65				
Superior frontal medial gyrus					R	8	8, 30, 38	4.52*				
Temporal												
Inferior temporal gyrus	L	20	−78, −34, −18	3.89								
Middle temporal gyrus					R	21	68, −44, 0	5.26*				
					R	21	68, −28, −20	4.42*				
Superior temporal gyrus									L	22	−46, −38, 14	3.33
Parietal												
Inferior parietal gyrus	R	40	58, −44, 50	4.06	R	40	58, −48, 42	4.46*				
	R	40	50, −46, 40	3.61								
	L	40	−50, −52, 46	3.59	L	40	−48, −46, 48	5.03*				
Supramarginal gyrus					R	48	50, −60, 46	3.46				
Precuneus									L	17	−32, −72, 18	3.17
Occipital												
Medial occipital gyrus									L	19	−52, −76, 0	3.62
Cerebelum	L		−38, −68, −26	4.26	L		−28, −68, −24	3.83	L		−46, −82, −20	4.04
	L		−48, −78, −24	3.68	L		−42, −64, −40	3.21				
Putamen	R		22, 14, 6	4.73								

* Regions for which the level of activation was also significant at $P \leq 0.001$, corrected for multiple comparisons.

TABLE VI. Brain regions where counting with no auditory stimulation showed relCBF increases when compared to rest in controls (patients and controls minus patients)

	Controls				Patients				Controls minus patients			
Region	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score
Frontal												
Precentral gyrus	R	6	48, −8, 30	5.16*					R	4	52, −6, 32	5.28
									R	4	38, −10, 48	2.87
Inferior frontal gyrus	R	44	60, 10, 20	4.75*	R	47	54, 40, −12	5.48*				
	L	44	−50, 8, 6	3.68*	R	45	58, 22, 2	4.63*				
	L	44	−70, 8, 26	3.57*	L	47	−42, 42, −4	3.34				
	L	44	−64, 4, 20	3.52								
Suplementary motor	R	6	6, 4, 70	4.62*	R	6	0, 16, 56	3.91	R	6	−2, −16, 56	3.60
									R	6	12, −8, 68	3.28
DLPFC	R	46	30, 48, 16	4.48	R	10	40, 52, −4	4.99*	R	10	12, 68, 4	3.60
	R	9	44, 30, 28	3.80	R	10	30, 58, 0	3.56				
	L	10–46	−48, 56, 4	3.59	L	9	−38, 32, 32	3.78				
					L	10	−22, 54, −6	3.39				
Cyngulate gyrus	L	32	−10, 12, 46	4.34*								
	L	32	−4, 8, 50	4.28*								
Medial area of superior frontal gyrus, midline					R	6	−8, −2, 62	3.27				
Temporal												
Middle temporal gyrus					R	21	68, −46, 0	4.5				
					L	20–21	−66, −28, 24	3.19				
Superior temporal gyrus									L	22	−46, −36, 16	3.30
Parietal												
Inferior parietal gyrus	R	40	58, −42, 48	4.31*	L	40	−48, −46, 46	3.77				
			46, −46, 38	3.93*	R	40	60, −42, 46	3.22				
	L	40	−42, −52, 40	3.37			58, −50, 40	3.20				
Supramarginal gyrus					L	39–40	−50, −60, −36	3.42				
					R	40	50, −60, 46	3.32				
Cerebelum	L		−38, −68, −28	4.35	L		−38, −66, −44	3.25				
Putamen	R		22, 14, 6	4.89*	R		28, 0, −2	4.57				

* Regions for which the level of activation was significant at $P \leq 0.001$, corrected for multiple comparisons.

TABLE VII. Brain regions where counting with no auditory stimulation showed higher relCBF increases than counting with auditory stimulation in controls, patients, and controls minus patients

	Controls				Patients				Controls minus patients			
Region	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score	Side	BA	Talairach coordinates	Z-score
Frontal												
Precentral gyrus	R	6	52, −6, 30	3.85								
	R	4	36, −4, 42	3.41	L	4	−64, −4, 30	3.08				
DLPFC	R	9	34, 14, 34	3.81					R	9	38, 38, 42	3.76
	L	10	−44, 56, 4	3.59					R	10	14, 70, 8	3.58
Inferior frontal gyrus					R	47	52, 28, −18	3.45				
					R	44	54, 10, 20	3.23				
					R	47–10	56, 38, −14	3.08				
					R	44	66, 8, 6	3.01				
Suplementary motor	R	6	2, 8, 48	3.05								
Posterior cyngulate gyrus	R	23	6, −30, 16	3.15								
	L	24	−8, 16, 24	3.14								
Anterior cyngulate gyrus									L	32	−10, 24, 28	3.17
Parietal												
Inferior parietal gyrus	R	40	46, −62, 46	3.51					R	39	46, −70, 34	3.15
			50, −44, 36	3.02								

left hemisphere for patients). Patients, as well as controls, activated right inferior frontal gyrus and right postcentral gyrus. When the differences between groups were analyzed, statistically significant levels of increased activation were obtained for controls on right DLPFC ($Z = 3.76$), left anterior cingulate ($Z = 3.17$), and right inferior parietal ($Z = 3.15$) (Table VII, Fig. 1).

DISCUSSION

Listening

Listening conditions demanded subjects pay attention to an external stimulus repeated at a constant rate of 1 click per second. When considering listening conditions, to analyze the main effect of listening we observed, for both groups, the activation of primary auditory cortex (transversal temporal region; with stress in left side) and medial temporal area. This data is consistent with results obtained from previous studies of functional neuroanatomy that link the transversal temporal and medial regions to auditory processing [Fiez et al., 1996; Holcomb et al., 2000]. The absence of significant differences when the levels of activation are compared between groups suggests a similar pattern of auditory processing for both. Differences between normal controls and patients with schizophrenia have been reported by investigators employing PET during auditory processing, but always during more complex dichotic tasks [O'Leary et al., 1996].

During listening tasks we also found the active participation of cingulate regions for both controls and patients. The relation between cingulate area and attention has a vast history of experimental support [Carter et al., 1997; Janer et al., 1991]. The cingular activation could be understood in terms of the attentional component of the tasks of listening where subjects have to keep track of the clicks during a preestablished time. For schizophrenics, the activation of both anterior and posterior cingulate adds an extra component of participation (overactivation) of cingulate region and medial frontal that has been reported repeatedly to be depressed in schizophrenia [Carter et al., 1997; Crespo-Farroco et al., 1999; Holcomb et al., 2000]. Additionally, for normal controls we observed the participation of superior parietal and temporal regions on listening conditions and the absence of such activation for patients during the same conditions.

We suggest that auditory processing is similar for both groups because they require the primary sensorial processing regions. Differences are observed in the associative and heteromodal cortex requiring patients to exhibit more activation of the cingulate and medial-frontal cortex.

Counting while listening

Our findings suggest that mental serial counting (for both samples) requires the participation of specific frontal regions (e.g., SMA, DLPFC, precentral, and

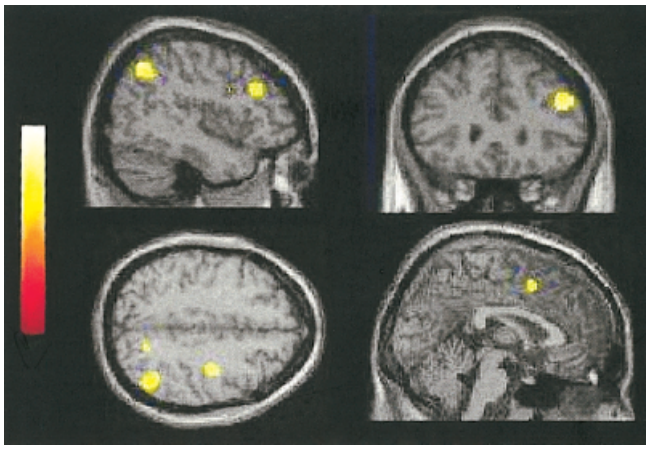

Figure 1.
Regions exhibiting significant relCBF increases during counting with auditory stimulation relative to counting with no auditory stimulation in controls.

cingulate), cerebellum, and inferior parietal region. These results partially replicate the findings of Cowells et al. [2000] for processes of simple number repetition. One unanticipated result was that while counting, patients with schizophrenia seem to engage additional frontal structures, including the inferior, medial, and superior frontal areas.

No specific cognitive effort is required by the subject when counting while listening to a monotonous and repetitive tone, because we seem to transform serial counting into an automatic type of information processing early in life. Authors have already described the relation observed among precentral, DLPFC, SMA, and counting [McCloskey et al., 1987, 1991]. In the specific case of this automatic processing, however, we observed the additional contribution of inferior and superior frontal regions as well as inferior temporal for both experimental and normal subjects. However, patients failed to significantly activate the superior temporal regions for automatic mental processing whereas there is a contribution of the inferior parietal region for the effective performance of this task.

Control processing vs. automatic processing: neuroanatomical basis

Different contributions by several cerebral regions during controlled and automatic processing have been observed in our study. Our findings underline the differential role played by four specific frontal regions (DLPFC, precentral cortex, SMA, anterior cingulate) and the inferior parietal during automatic and control processing tasks. Our naïve patients failed to activate some prefrontal regions and inferior parietal cortex at a similar level during a task that required additional cognitive effort. This fact cannot be explained by different cognitive performances in brief time estimation and working memory during Task C, as calculated differences between group performances were not significant.

DLPFC

The control component in our study is defined by working memory and time estimation factors. The relation between DLPFC and working memory tasks has been reported previously [Miller, 2000]. The direct relation between the DLPFC and "willed action" (when responses have to be selected by the subject without the help of any external clue) was first described by Petrides et al. [1993] and later confirmed by different authors [Frith et al., 1995; Artiges et al., 2000; Bertolino et al., 2000; Jahanshani et al., 2000; Menon et al., 2000].

The idea of the central executive developed by Baddeley [1986] and the SAS [Shallice, 1988] seems to have much in common with these findings. Far from concluding that the DLPC is the seat of willed action, however, our data seems to suggest the participation of these regions together with other areas, such as cingulate and precentral gyrus. During the counting while listening condition (the rate of serial counting is externally provided), an inferior level of activation of

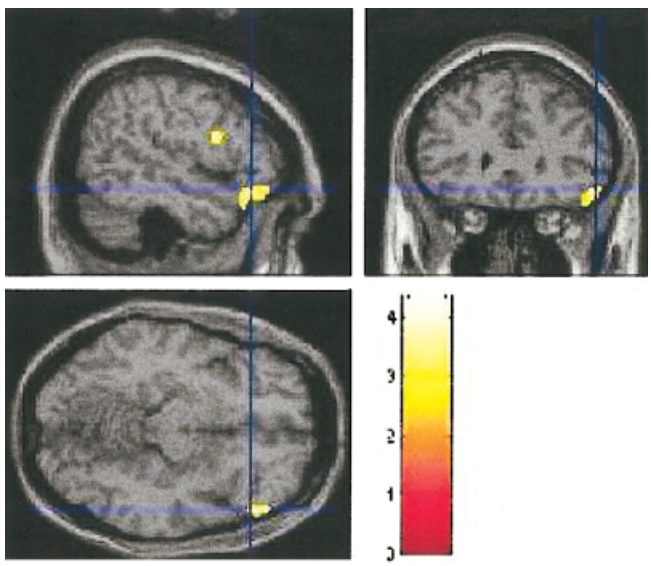

Figure 2.
Regions exhibiting significant relCBF increases during counting with auditory stimulation relative to counting with no auditory stimulation in naïve patients with schizophrenia.

the DLPFC region was observed. One possible explanation for this observation could be that when the cognitive task is no longer novel, i.e., learning has occurred, there may be suppression of attention (or diminished attention) to information that is no longer relevant. We confirm the implication of DLFPC when working memory and increased attention are required in tasks relating to auditory stimuli presented previously. Moreover, during the Task C condition, subjects had no need to process information of any sensorial modality. For that reason, we suggest the participation of DLPFC during non-routine tasks independent from the sensorial modality in normal subjects, and the significantly minor level of activation in DLPFC for the same tasks in patients with schizophrenia [Callicott et al., 1988]. Previous authors have reported deficiencies in quality responses when patients with schizophrenia had to make decisions with a time interval major to 1 second [Tracy et al., 1998, 2000]. We also confirm the altered participation of the frontal structures in patients with schizophrenia when the cognitive task includes a time estimation component equal to 1 second.

Cingulate

Evidence from results obtained in this study indicate general dismissed cingular activation when patients are compared to controls during all counting conditions. Initially, the lack of cingulate activation for both groups, as obtained from the subtraction of Task A from Task A+C, was not expected. The lack of significant levels of activation after the subtraction do not necessarily mean the complete lack of activation, but could be indicative of similar levels of activation for both samples as observed when data is analyzed separately for each group and condition. Posner [1995] has argued persuasively that anterior cingulate cortex is involved in controlled attention (attention that is deliberately and consciously directed rather than simply being captured by salient events). Tzourio et al. [1997] has reported increased activation of cingular region during auditory attention tasks for normal subjects. Jones et al. [1997] described significant increases in relCBF in the thalamus and anterior cingulate, but not DLPFC, during processing of painful stimulus on normal controls. Similar activation has been reported in studies of focused attention to other somatosensory and visual signals [Pardo et al., 1991]. For that reason, the implied participation of the anterior cingulate could be related to the attentional component itself rather than the sensorial modality. In our study, participation of the anterior cingulate (ACC) in normal subjects was not observed equally in all conditions that required focused attention. Moreover, during the listening condition, normal subjects activated the posterior but not anterior cingular region; on the other hand, anterior (and posterior) cingular activation was observed in the group of patients during the same condition. From these data, there is not enough evidence of the participation of the cingulate area in attentional processes independent of the type of attention required. For example, Corbetta et al. [1991] reported ACC activation during tasks of divided attention, but not selective attention conditions, during a visual task; the absence of ACC activation and increases in relCBF in SMA during automatic responses was also reported. Our observation of increases of SMA and cingular activation during counting and listening seems to support the idea of the participation of both structures in some but not all cognitive tasks requiring attentional effort.

DLPFC and ACC

Paus et al. [1993] suggested that ACC and DLPFC were involved equally in processes requiring response selection. Activity at ACC and DLPFC has been related to cognitive control. Both structures seem to participate when subjects perform a task that requires working memory or when more than one task is demanded at the same time. Although both ACC and DLPFC might be part of what Posner and Petersen [1990] called the "executive attentional system," it seems to be further evidence of the different participation and dissociation of the ACC or DLPFC. MacDonald et al. [2000] argued the major participation of DLPFC during cognitive control tasks (complex and novel tasks), and the increasingly higher participation of ACC in processes of monitoring cognition. Taken together, the data could suggest that cognitive control is a dynamic process implemented in the brain by a distributed network that involves closely interacting but anatomically dissociable components. Within this system, the DLPFC provides top-down support of task-appropriate evaluative processes, indicating when cognitive control needs to be more strongly engaged [MacDonald et al., 2000]. From our results, it seems reasonable to conclude that this control system is altered in schizophrenia.

Frontal structures

Parallel to the dismissed activation of ACC and DLPFC for more demanding conditions, our results also show the overactivation of other frontal struc-

tures in patients, above the levels observed for normal controls, particularly in the case of the inferior frontal region. From our results we can conclude a similar pattern of activation between controls and schizophrenic participants for frontal regions during simple cognitive tasks, with the participation of DLPFC, precentral gyrus, inferior and superior regions, and supplementary cortex. During more cognitively complex tasks, however, differences were observed for the participation of frontal regions: significant activation was observed in DLPFC, precentral and SMA for normal controls, whereas significantly superior activation at inferior frontal area was observed in patients. Normal volunteers showed increased activation of DLPFC, precentral, AMS and cingulate regions in response to increased demand. Patients failed to sufficiently activate these structures and seemed to need the compensation and support of other frontal regions, such as inferior frontal, to respond (compensation hypothesis). This data could be suggestive of a differential pattern in the way that patients modulate their brain activity according to task demand. A similar differential pattern of response between controls and patients for control tasks has been reported previously by Holcomb et al. [2000].

Parietal lobes

As reported, patients significantly failed to activate inferior parietal (IP) during cognitively demanding tasks. The participation of parietal regions (posterior area) in cognitive tasks requiring effort was described by Posner and Petersen [1990]. Posner proposed a network between the posterior parietal and medial-lateral frontal cortex, the "posterior attention system," which participates when the subject needs focused or conscious attention. It would be reasonable to think that the double task of listening and counting in our experimental paradigm would require a mental effort for subjects with schizophrenia, although it would still be an automatic process for normal subjects. Normal subjects activate IP when a cognitive effort is needed, as in the control processing request in C. Other studies have also reported parietal lobe participation and the link to DLPFC during cognitive tasks that require auditory working memory and control processing [Menon et al., 2000].

Laterality

Overall, our results suggest diminished advantage for the left hemisphere (right hemisphere dominance) in patients for all conditions analyzed. This left–right differential ratio is especially significant in auditory processing conditions when compared to controls, for whom the lateralization to left hemisphere is higher at the listening conditions (auditory attention). Laterality effects in audition were suspected previously [Millner, 1962] in normal subjects and later evidenced through neuroimaging studies in monkeys [Pehune et al., 1996]. Our data add support to functional neuroimaging data published previously [Fallgatter et al., 2000; Higashima et al., 2000; Malaspina et al., 2000] indicating altered (higher) left activation in patients during auditory attention tasks. This imbalance during cognitive activities has led some investigators to hypothesize that schizophrenia may be a hemispheric disorder.

We observed differences in the activation of frontal structures, depending on the cognitive demand, for naïve patients with schizophrenia. These data support the idea of overactivation of specific frontal regions (i.e., cingulate, inferior frontal), parallel to observed deficiencies in activated brain areas in normal subjects. Additionally, we suggest a differential pattern of activation in patients, which includes parietal cortices, during cognitively demanding tasks. Taken together, these data could be indicative not only of hypoactivation of specific brain regions or circuits in schizophrenia, but also of differential and compensatory mechanisms integrated by fronto-parietal structures.

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