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Short Communication

A Test-retest Study of Cerebral Blood Flow During Somatosensory Stimulation in Depressed Patients with Schizophrenia and Major Depression

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Summary. Six depressed patients with schizophrenia and 6 depressed patients with major depression were investigated before and during somatosensory stimulation (SS) with Tc-99m HMPAO SPECT. 8 controls were investigated only under resting conditions. The results can be summarized as follows: 1. Both psychiatric patient groups were hypofrontal (dorsolateral prefrontal cortex) compared to controls. 2. Hypofrontality was further enhanced by SS, significantly only in affective psychoses in the right inferior frontal lobe and in the right frontal hemisphere in total, in schizophrenia in the left dorsolateral prefrontal cortex. 3. Within the frontal lobes different regions were affected by SS in the two diagnostic groups. 4. In the right inferior parietal lobe SS response was significantly different in the two illnesses with schizophrenia showing a relative decrease, affective psychoses showing a relative increase of activity. 5. SS produced an increase of cerebral blood flow in subcortical regions (statistically significant contralateral to SS in thalamus and basal ganglia, ipsilateral to SS in cerebellum), a pattern which was common to all psychiatric patients. 6. Somatosensory cortex flow was not changed by SS. In conclusion, we could not fully confirm our hypotheses that similar blood flow abnormalities in different illnesses during SS are only caused by similarities in depressive psychopathology. Instead, depressed patients with schizophrenia were different from depressed patients with major depression in showing decreased activity in interrelating brain regions participating in an attentional network.

Key words: Somatosensory stimulation – SPECT – Schizophrenia – Major Depression – Hypofrontality – Right inferior parietal lobe

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Introduction

Consequences of somatosensory stimulation (SS) for cerebral metabolism have not been fully characterized. During SS normals had higher contralateral postcentral activity than those during rest (Greenberg et al. 1981, Buchsbaum et al. 1983). As SS also activates selective attention and may induce cognitive reactions to environmental stimulation, blood flow changes would not be expected to be limited to the primary somatosensory areas, but might involve affective, association, and cognitive areas associated with feeling, planning, and coping (Buchsbaum et al. 1983). Indeed, SS additionally revealed a pattern of frontal lobe increases in normals (Ingvar et al. 1976, Buchsbaum et al. 1983). Patients with schizophrenia and affective disorders, however, were hypofrontal during SS compared to controls and did not show a localized contralateral response (Buchsbaum et al. 1984). From previous studies it cannot be clearly stated whether hypofrontality in psychiatric patients is really induced by SS, or only due to baseline hypofrontality with 'normal' frontal activation, as no test-retest design has been used. It is also open to discussion, that Buchsbaum et al. (1984) had not found major differences between schizophrenia and major depression. As only chronic schizophrenics with predominant affective symptomatology were investigated, it can be hypothesized that possibly depression is the generalized feature of both illnesses correlating to relative hypofrontality. Beyond this hypotheses it remains open to question, whether blood flow responses to SS differ between different diagnostic entities, and how SS effects common to all diagnostic groups may be characterized in a test-retest design.

To test this hypotheses, that diagnostically unspecific depressive states are connected to hypofrontality during

SS as an underlying pathophysiological process, we investigated depressed patients of same affective psychopathology, but different origin with HMPAO SPECT in a test-retest design before and during SS. The questions asked were as follows: What are the overall SS effects in all depressed patients? Is the SS response different in different diagnostic groups?

Methods

Six in-patients with bipolar disorder, depressed (295.6 according to DSM-III-R, female/male 5/1, 42.2 years ± 12.5, Hamilton Depression Scale, 21-items, 23.2 ± 3.8, all medicated with 200–400 mg sulpiride and 75–150 mg amitryptiline for at least 2 weeks) and 6 in-patients with schizophrenia, residual type, depressed (296.5 according to DSM-III-R, female/male 4/2, 39.2 years ± 11.1, Hamilton Scale 24 ± 5.8, all medicated with 200–400 mg sulpiride and 75 mg amitryptiline for at least 2 weeks) participated in the study after informed consent had been obtained. In the AMDP system (1979), all patients had a depressive syndrome, medium or severe. The two groups differed as follows: in schizophrenia ratings were higher for attentional deficits, flattened affect and paranoid ideas, but lower for vegetative disturbances and disturbances of vital feelings and daily rhythms.

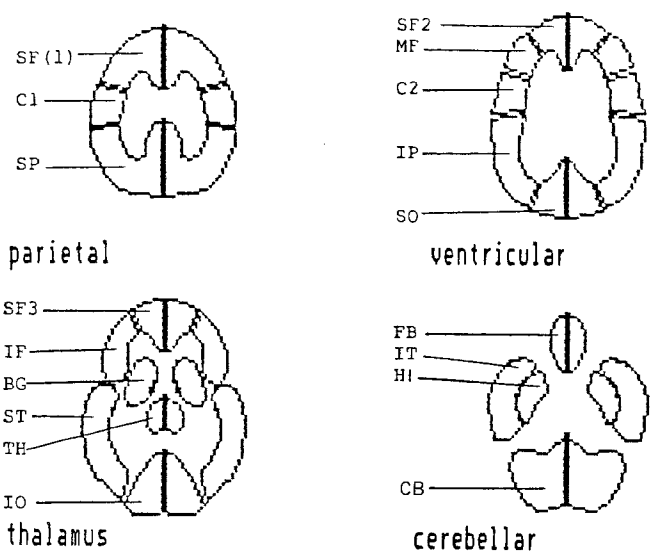

Fig. 1. Diagram of the 18 regions of interest in four slices. Abbreviations: SF 1, 2, 3: pre-frontal (upper, medium, lower parts), MF: medial frontal, IF: inferior frontal, FB: frontoorbital, C 1, 2: central, SP IP: parietal (inferior, superior), SO, IO: occipital (superior, inferior), ST, IT: temporal (superior, inferior), BG: basal ganglia, HI: hippocampus, TH: thalamus, CB: cerebellar

All subjects were investigated twice with Tc-99m-HMPAO SPECT. SPECT 1 was performed under resting conditions (eyes closed, quiet room), SPECT 2 with SS 48 h later. Psychopathological ratings kept unchanged between the two measures.

Somatosensory stimuli consisted of electrical impulses of 0.2 ms duration and 0.5 c/s frequency delivered to the right median nerve at the wrist and achieving a clear motor response of the thumb. Stimulation was performed for 1 min before and 10 min after the injection of HMPAO.

SPECT was performed with a Siemens double-headed Rota-Camera with high-resolution collimators, rotation angle 6°, acquisition time 60 s/angle, 64 × 64 matrix, reconstruction with Butterworth filter of transversal, of oblique and coronal, and also of sagittal slices. For semiquantitative evaluation an algorithm of Podreka (1987) was used, condensing brain data between parietal and lower cerebellar pole into four slices. Eighteen anatomically significant areas (regions of interest) were depicted, mirrored into the other hemisphere and corrected if necessary (Fig. 1). For each region a Regional Perfusion Index (RPI) was calculated as ratio of counts per voxel of one region/counts per voxel of all brain regions. Additionally, an RPI for all six frontal regions was calculated as a global index for hypofrontality. SPECT methods, regions of interest, and applications of methods in clinical studies are also described elsewhere (Feistel et al. 1989, Ebert et al. 1991).

Group differences of SS response between schizophrenia and major depression were compared with *U*-tests, overall test-retest effects for all 12 patients and for the two diagnostic groups separately with Wilcoxon tests. SS response was defined as RPIs during SS minus RPIs before SS.

The pre-SS baseline RPIs of the two patient groups were additionally compared with eight healthy controls (4 women, 4 men, 41.5 ± 10.2 years) by Kruskal-Wallis tests and post-hoc *U*-tests. No second post-SS investigation was possible for ethical reasons. However, this procedure still gives some information about baseline blood flow in psychiatric patients compared to controls for appropriate interpretation of SS changes.

Results

Both groups of psychiatric patients were hypofrontal compared with controls. Comparisons were statistically

Table 1. The frontal lobes. Regional perfusion indices under basal conditions and the changes during SS (SS change = perfusion index during SS minus perfusion index before SS) of all six frontal regions (frontal total) and the two regions with statistically significant between-group differences and differences between patients and controls. * = $P < 0.05$ *U*-test: schizophrenia or major depression vs. controls. ⋆ = $P < 0.05$ *U*-test: SS change schizophrenia vs. major depression. Underlined SS changes = $P < 0.05$ Wilcoxon-test: perfusion index before SS vs. perfusion index during SS. All other comparisons not significant. Controls were investigated only once

		Schizophrenia ($n = 6$)	Major depression ($n = 6$)	Controls ($n = 8$)
Frontal total	Right	98.1 ± 4.3	98.0 ± 3.7	102.0 ± 3.5
	SS change	−7.4 ± 3.5	−11 ± 2.4	–
	Left	96.6 ± 5.1	97.3 ± 3.0	99.1 ± 4.7
	SS change	−3.2 ± 1.3	−5.2 ± 2.6	–
SF2	Right	100.8 ± 4.5	99.2 ± 3.7	109.5 ± 3.7
	SS change	−0.8 ± 0.6	+0.8 ± 0.5	–
	Left	98.6 ± 4.3*	97.8 ± 3.7*	110.0 ± 2.8
	SS change	−3.5 ± 1.0⋆	+0.2 ± 0.8⋆	–
IF	Right	96.5 ± 8.3	100.6 ± 2.4	107.0 ± 3.5
	SS change	+3.7 ± 1.9⋆	+6.0 ± 1.5⋆	–
	Left	94.5 ± 5.7	97.8 ± 3.3	103.5 ± 2.8
	SS change	+2.7 ± 2.0	−1.2 ± 0.5	–

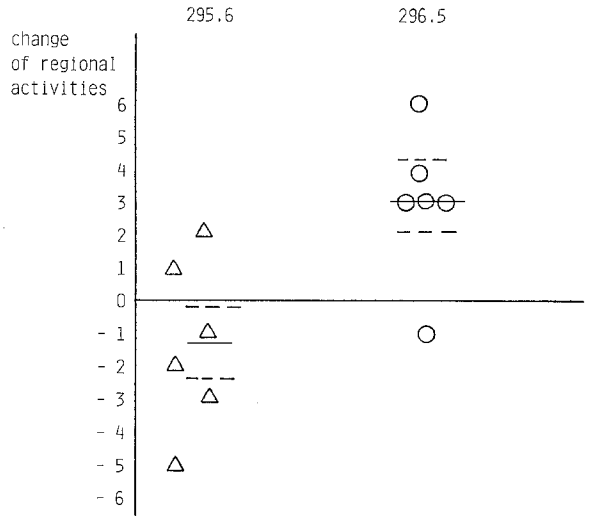

Fig. 2. The right inferior parietal lobes. Change of Regional Perfusion Indices (Perfusion Index during SS minus Perfusion Index before SS) in schizophrenia (295.6, according to DSM-III-R) and major depression (296.5, DSM-III-R) $P<0.05$ with U-Test: SS change schizophrenia (-1.3 ± -1.1) vs. SS change major depression ($+3.0 \pm 1.1$). Test-Retest difference in Major Depression $P<0.05$ with Wilcoxon-Test

significant ($P<0.05$) only for the left and right dorsolateral prefrontal areas SF 2 (Table 1). No other comparisons between patients and controls were significant.

A decrease of global frontal activity during SS was present in both groups reaching significance ($P<0.05$) only in affective disorders on the right (Table 1). Both groups had different response patterns within the frontal lobes: in schizophrenia frontal decrease was most prominent in the left dorsolateral pre-frontal area (schizophrenia: -3.5 ± 1.0, $P<0.05$ within Wilcoxon test; major depression: $+0.2 \pm 0.8$; not significant), in affective disorders in the right inferior frontal lobe (schizophrenia: $+3.7 \pm 1.9$, not significant; major depression: -6.0 ± 1.5, $P<0.05$ with Wilcoxon test). For these two regions the SS responses in the two groups were significantly different (U-test, $P<0.05$, Table 1).

As seen in Fig. 2, the two groups showed another significantly different SS response in the right inferior parietal lobe ($P<0.05$ U-test schizophrenia vs. major depression) with schizophrenics having a relative decrease during SS (-1.3 ± 1.1) and affective disorders having a relative increase ($+3.0 \pm 1.1$, test-retest change $P>0.05$ with Wilcoxon test).

There were some regional relative increases of cerebral blood flow during SS, which were common in all patients. Table 2 shows these regions with statistically significant test-retest changes: Thalamus, basal ganglia, cerebellum.

Discussion

The results can be summarized as follows: 1. Both psychiatric patient groups were hypofrontal (dorsolateral pre-frontal cortex) compared to controls. 2. Hypofrontality was further enhanced by SS, significantly only in affective psychoses in the right inferior frontal lobe and in the right frontal hemisphere in total, in schizophrenia in the left dorsolateral pre-frontal cortex. 3. Within the frontal lobes, different regions were affected by SS in the two diagnostic groups. 4. In the right inferior parietal lobe, SS response was significantly different in the two illnesses with schizophrenia showing a relative decrease, affective psychoses showing a relative increase of activity. 5. SS produced an increase of cerebral blood flow in subcortical regions (statistically significant contralateral to SS in thalamus and basal ganglia, ipsilateral to SS in cerebellum), a pattern which was common to all psychiatric patients. 6. Somatosensory cortex flow was not changed by SS.

All patients were medicated. Thus, comparisons with controls under baseline conditions and test-retest effects of SS may be influenced. In a previous study, neuroleptics induced changes in thalamus and basal ganglia, not in anterior-posterior gradients; however, medication effects on cerebral blood flow are not fully characterized so far (Buchsbaum et al. 1987). In a recent review, the authors (Weinberger and Berman 1988) concluded that there were at present no compelling data to implicate medication status as the primary determinant of hypofrontality. It was their view that other state-related variables were more important. For interpretation of our data it has to be considered that differences between the two stimulated groups are probably not due to medication, as the same medication has been applied in both illnesses. Similarily, age, sex distribution, and depressive psychopathology probably do not account for differences in SS response, as there were no differences evident between the two patient groups.

As the subcortical regional changes in thalamus and basal ganglia were in accordance with the proposed

Table 2. Change of regional perfusion indices (m ± sd, regional perfusion during SS minus regional perfusion before SS) of the brain regions with statistically significant increases of cerebral blood flow during somatosensory stimulation (either in one patient group or the total sample).
* = $P<0.05$ Wilcoxon-test: within-group comparisons before SS vs. during SS.
TH = thalamus, BG = basal ganglia, CB = cerebellum

		Schizophrenia ($n=6$)	Major depression ($n=6$)	All ($n=12$)
TH	Right	$+3.3 \pm 2.2$	$+1.4 \pm 2.3$	$+2.4 \pm 2.3$
	Left	$+4.5 \pm 1.9$	$+3.0 \pm 1.0$*	$+3.8 \pm 1.5$
BG	Right	$+3.8 \pm 2.9$	$+4.6 \pm 3.2$	$+4.2 \pm 3.0$
	Left	$+6.3 \pm 2.6$	$+9.4 \pm 4.3$	$+7.9 \pm 3.5$*
CB	Right	$+5.0 \pm 2.4$*	$+1.0 \pm 1.0$	$+3.0 \pm 1.7$*
	Left	$+4.3 \pm 1.7$	-0.6 ± 1.3	$+1.9 \pm 1.5$

neuroanatomy of a basal ganglia loop as primary sensory pathway (Martin 1989), we believe these changes to be the physiological cerebral blood flow response to sensory stimuli independent of psychiatric illness. This interpretation is further strengthened by the finding that left contralateral thalamus and basal ganglia were more activated than right parts of the proposed basal ganglia loop by right-sided SS. Similarily, ipsilateral cerebellar increase may reflect tactile components of SS. These activity increases in subcortical, primary sensory pathways, which have not been studied extensively in previous studies, also provide a notion of the power and sensitivity of SPECT methodology.

The missing SS response in (contralateral) somatosensory cortex could not be expected from investigations of normal controls or our knowledge of physiologic processes. However, it does indeed support previous findings in psychiatric patients (Buchsbaum et al. 1984). One possible explanation argues that affective symptomatology and psychiatric disease may lead to a disseminated and diffuse, non-localized cortical response to stimuli independent of diagnostic entities. Corresponding arguments have been put forward as explanations for relative hypofrontality with diffuse overactivation of posterior cortical regions during SS due to various diffuse system projections to the cortex, which are activated by psychiatric illness (Buchsbaum et al. 1984). Some further support comes from another investigation finding a diffuse, non-localized activation pattern to motor, not sensory stimuli, in type-II schizophrenics with affective symptoms compared to type-I-schizophrenics or controls (Günther et al. 1991).

The given interpretations of Buchsbaum et al. (1984) may also be applied to the following results concerning the frontal lobes and their SS response. Under basal resting conditions, we found hypofrontality in schizophrenia and major depression compared with controls. When investigating single frontal regions only the left dorsolateral pre-frontal cortex was hypoperfused in both groups. This result is in accordance with previous studies finding left pre-frontal hypoactivity in schizophrenia (Buchsbaum et al. 1984, 1990, Weinberger et al. 1988), as in depression (Baxter et al. 1985, Martinot et al. 1990, Ebert et al. 1991), as a kind of common marker of psychiatric illness or affective psychopathology.

Our test-retest data also support previous studies finding hypofrontality in schizophrenia and affective disorders during SS compared to controls (Buchsbaum et al. 1984). SS reduced total relative frontal activity in both disorders, though basal pre-SS frontal perfusion was already low compared with controls. However, statistical significance was reached only by right sided affective disorders.

The single regions participating in inducing hypofrontality were different in the two psychiatric illnesses, though sharing common psychopathology. In affective disorders, perfusion was reduced significantly only in the right inferior frontal parts. Another study also found reduced tracer uptake in the inferior frontal cortex in major depression (Austin et al. 1992); however, the functional implications of this region for affective disturbances remain open to debate so far. In schizophrenia SS-reduced blood flow in the dorsolateral pre-frontal cortex was significantly different from affective psychoses. These results in the pre-frontal area have to be interpreted together with the decrease of activity in the right inferior parietal lobe during SS, seen in schizophrenia compared with affective disorders. As summarized elsewhere (Asarnow 1982, Mirsky and Duncan 1989, Buchsbaum et al. 1990), the attentional network includes interrelated brain areas with the pre-frontal and temporoparietal components playing an important role. The pre-frontal cortex supports planning and executive functions, including shifts of attentional focus, the right inferior parietal lobule is a polymodal sensory convergence area that is hypothesized to play an important role in focusing on a target stimulus, implicating selective attention. Unilateral visual stimulation increased metabolism of the right inferior parietal cortex, independent of the side of visual stimulation (Volkow and Tancredi 1991); the same increase was evident in subjects performing the Continuous Performance Test (Buchsbaum et al. 1990). Thus, we postulate that the decrease of activity in left pre-frontal and right parietal regions in our schizophrenic group is a non-physiological response to the attention activating SS procedure. Thus, it can be concluded that our data reflect attentional deficits in negative schizophrenia, which are not just connected to depressed affect. This is in accordance with neuropsychological studies finding differences between schizophrenia and affective controls in attention activating tasks (for a short review, see Buchsbaum et al. 1990). Buchsbaum et al. (1990) found a right hypoparietal pattern in schizophrenics during the Continous Performance Test with PET. Others could show reduced right parietal activity in schizophrenia also under resting conditions with PET (Kishimoto et al. 1987, Cleghorn et al. 1989).

In conclusion, we could not fully confirm our hypotheses that similar blood flow abnormalities in different illnesses during SS are only caused by similarities in depressive psychopathology. Instead, depressed patients with schizophrenia were different from depressed patients with major depression in showing decreased activity in interrelating brain regions participating in an attentional network. For future research it is concluded that further investigations should be carried out during specifically attention activating tasks.

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