Mood and cerebral perfusion revisited

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Twenty patients with major depression and observed diurnal variations of mood were examined using clinical and neuropsychological measures and perfusion HMPAO-SPECT at 8 a.m. and 8 p.m. In thirteen patients depression scores varied more than 15% between both measures, although 4 patients with reverse diurnal variation caused mean group depression scores to be not different between morning and evening. There was an overall trend for higher depression scores to be associated with higher perfusion in posterior cingulate. This was mainly accounted for by significant positive correlations in the morning scan in posterior, but also anterior cingulate and medial prefrontal cortex compared with evening scans. This means that morning regression slopes were steeper than evening slopes. This result is discussed with regard to possible interpretations, such as adaptive or habituating changes during the day that may occur in depressed patients.

1. Introduction

Evidence accumulated in affective disorder research over the last five years points towards the limbic frontal lobes, including the (anterior) cingulate, the basal ganglia and parts of the temporal lobe (such as the amygdala) as structures underlying symptom formation [24]. This evidence partly derives from cross-sectional association studies. However, in order to demonstrate the association between symptoms and brain activity more convincingly, repeat-measures analyses that can link brain activity with symptom changes are necessary. Unfortunately, such studies tend to suffer from order effects that occur, for example, when patients are examined before and after treatment, i.e. first ill and then recovered [22]. As a matter of principle, changes in such studies can be due to regression to the mean or habituation effects that confound the observed associations between symptoms and brain activity patterns. For economic reasons, balancing studies for order by examining subjects first when well, is impossible apart from very rare occasions, such as lithium withdrawal

studies or symptom provocation with tryptophan depletion, where deterioration in clinical state can be predicted [5,20,31]. Prospective single-scan designs have been used, trying to validate pre-treatment brain activity maps by treatment response or outcome measurements [28]. While such longitudinal studies are an improvement on simple cross-sectional association studies, their main disadvantage is that effects are based on comparison between-subjects, which in selected samples of depressed patients are liable to confounding with other spurious differences of the compared groups. Mood induction experiments can be conducted in healthy volunteers with due control of possible order effects. Although the logical step from induced mood in healthy volunteers to mood changes in affective disorders may appear tenuous, remarkable similarities in brain-behaviour relationships have been described [2,3,8,25,29,36]. Finally, psychological tasks during image acquisition have been employed in depressed patients and during mood induction. If there is a diagnosis or mood specific activation pattern, it tends to be associated with poor performance of the task [2,15,16]. Consequently, the localisation of change is determined as much by the psychological task demand as by the mood change. In particular, no localisation of mood related changes could be derived from such studies.

In the present study, which has been reported in less detail previously [13], we exploit the natural diurnal variations in symptom severity that occur between morning and evening in some depressed patients. Such measurable variations in mood are accompanied by parallel changes in neuropsychological performance and even motor strength, which suggest that pervasive changes in brain activity take place within 12 hours [30, 34]. The advantage of this design is that patients are their own controls as far as socio-demographic variables are concerned. The same is true for medication and severity of depression. Finally, the order of examination can be balanced as far as morning or evening first examination is concerned.

2. Methods

Twenty unipolar patients with a diagnosis of major depressive episode with melancholia [1] were exam-

ined. There were 8 men and 12 women, with a mean age of 44 years (SD: 12). Their premorbid IQ, estimated with the National Adult Reading Test-Revised [32], was 109 (SD: 10). Three patients were left-handed, 17 right-handed as determined with the Annett Handedness Scale [6]. Illness severity was estimated with the Hamilton Depression Rating Scale (17-item [23]) and was 26 (SD: 6). The mean duration of episode at the time of examination was 44 days (SD: 62). Five patients were medication free at the time of imaging, 15 were medicated: 6 on neuroleptics, 2 on endocrine replacement (thyroxin), 1 on lithium carbonate, 14 on antidepressants, 1 on hypnotics and 2 on anxiolytics. The drug regime had been stable in the previous two weeks.

Patients were examined twice within 12 hours, half at 8 a.m. first and 8 p.m. second, the other half in reverse order. At both times, the following assessments were carried out:

(1) The Befindlichkeitsskala (BFS [38]) is an adjective check-list designed to measure short-term variations of mood, with two parallel versions and subscales for depression and fatigue.

(2) The Alderley Park State Anxiety Questionnaire (APSAQ [39]) is a self-rating scale, which was administered immediately after the injection of tracer.

(3) The Stress Arousal Inventory (SAI [27]) is an adjective checklist with two separate scales for stress and arousal.

(4) The Digit Symbol Substitution Test (DSST [40]) is a test of psychomotor speed. Two parallel versions were constructed from the original form.

(5) The Auditory Verbal Learning Test [26,35] is a verbal memory test using a read 15-item word-list, which has to be recalled immediately, and recalled and recognised after 30 min. Two parallel versions were used [7].

(6) Each subject was therefore asked to squeeze a dynamometer as hard as they could; the measures for three attempts were averaged.

Subjects were imaged with the Neuro 900 scanner (Strichman Medical Equipment Inc., Boston, USA). Each subject received 2×250 MBq of 99mTc-exametazime (HM-PAO). During the injection, patients were comfortably resting on the imaging table with eyes closed and covered, and environmental noises kept to a minimum. Slices were acquired parallel to the orbito-meatal plane starting at a level approximately 2 cm above the orbito-meatal (OM) line and at 1cm intervals above this level. Further details of the method have been described previously [13,14].

Images were processed following this pattern:

1. Manual yaw, roll and pitch correction of images was followed by an automated least-mean-square co-registration of image-pairs from the same subject in the SME scanning software (Neuro 900 version 2.92). Images were then edited to ensure they contained the same number of slices over equivalent brain volumes.

2. Images were exported as binary files and converted to Analyze format.

3. The first scan was decay-corrected and subtracted from the second scan, to produce an activity map reflecting the brain state at the time of the second injection.

4. The scan pairs were spatially normalised using a 12-point linear affine transformation into Talairach space (using SPM′95, cf. [13]). The transformation elements were derived from the average of both scans from each subject and applied to each identically [18]. The images were then smoothed with a (12 mm FWHM) Gaussian filter in three dimensions in order to reduce the error variance associated with individual variability in gyral anatomy and to improve the signal to noise ratio.

5. In order to take advantage of the improved treatment of multiple comparisons in SPM′96, data were re-analysed with SPM′96 using a blocked ANCOVA design (one block per subject) with two conditions (morning/evening). Global brain activity and age effects were removed using analysis of covariance. The psychometric covariate (BFS) was modelled separately for each condition. Tests were computed for main covariate effects, i.e. significant correlations of BFS scores with cerebral perfusion across conditions (8 a.m. and 8 p.m.) and for the interaction between covariate and condition, i.e. testing the hypothesis that regression slopes of regional perfusion on BFS scores were different in the morning and evening (not testing for significant correlations of symptom changes with change in perfusion as erroneously claimed in the 1997 paper [13]). The hypothesis that changes in perfusion were correlated with changes in mood was tested by removing between-subject variability from BFS scores (by subtracting subjects' mean scores from morning and evening scores), and modelling the interaction between this difference score and condition (8 a.m./8 p.m.).

Effects are reported as significant if they are considered to be so a posteriori using the algorithms of SPM′96. These take into account the total volume tested, the smoothness of the data, the magnitude of effects (expressed as z-values) and the spread of effect, expressed as volume with z above a certain value (usually with $p < 0.01$).

As there were a priori hypotheses relating to changes in fronto-limbic structures described in [13], such changes are reported if uncorrected z were significant at the $p = 0.001$ level.

For this paper, data were analysed and displayed using SPM′96 on Sun SPARC workstations and SPM for Windows Version 1.01, coded by Sergey Pakhomov and Nick Tsyganov (1997) on PCs.

The study followed a protocol approved by the Lothian Psychiatry and Psychology Ethics Sub-Committee and the Administration of Radioactive Substances Advisory Committee (ARSAC) at the UK Department of Health.

3. Results

As reported previously, there was no significant mean change in symptom scores between morning and evening. This was due to reverse 'atypical' diurnal changes in at least four of the 13 patients whose BFS was more than 15% different between evening and morning. In spite of the absence of mean mood changes across the sample, certain measures, such as DSST performance and maximum voluntary hand contraction were significantly worse in the morning [13]. This is not a normal physiological effect, as diurnal changes tend to go in the opposite direction in normal volunteers [30]. The absence of a significant overall mood difference between morning and evening in the group allowed for an assessment of mood change independently of the confound of 'time of day'. Figure 1 presents absolute percentage changes (i.e. disregarding the direction of change between morning and evening) for the neuropsychological and psychiatric measures employed.

As expected, there were no condition (8 a.m. versus 8 p.m.) effects on perfusion. At the corrected significance level of $p = 0.05$ there were no main effects of covariate, although there were positive correlations in posterior cingulate, consistent with the interaction effect described below (16, −70, 12; $Z = 2.99$, $p = 0.001$, uncorrected).

The only significant effect after correction for multiple comparisons was the interaction of condition with covariate, in the sense that correlations between BFS and perfusion were significantly greater in the morning than the evening. This effect was observable in posterior cingulate (−2, −50, 16; $Z = 3.66$; $p = 0.009$, corrected), and at lower levels of significance also in anterior cingulate/prefrontal cortex (24, 32, 12; $Z = 3.78$; $p = 0.025$, corrected; −34, 18, 32; $Z = 4.18$; $p = 0.049$, corrected). Not significant after correction, but possibly predictable were similar effects in right and left basal ganglia.

Significantly greater correlations in the evening could be observed in the right insula (28, −8, 16; $Z = 3.75$; $p < 0.0005$, uncorrected), although this effect was perhaps less predictable and clearly requires replication.

4. Discussion

The statistically strongest effect observed is the interaction between time-of-day and severity-of-depression measured by the Befindlichkeitsskala. It represents a stronger positive association between depression and limbic brain perfusion in the morning compared with the evening (Fig. 2) and survives rigorous correction for multiple comparisons. This is particularly interesting, as the mean BFS (and its variability) did not change from morning to evening in our sample (morning – mean: 38, SD: 14; evening – mean: 39, SD: 12 [13]). The difference is, therefore, unlikely to be due to a simple floor or ceiling effect. A time-of-day dependent 'uncoupling' of the symptom-brain activity relationship in certain areas of the limbic cortex may suggest compensatory brain mechanisms or a habituation of such mechanisms during the course of the day.

It may also explain some of the difficulties encountered in studies trying to replicate cingulate and medial prefrontal changes in depressed patients [9]. Interestingly, the most convincing positive associations of depressive symptoms with medial anterior perfusion come from short-term repeat-measures studies in depressed patients or controls [10,19,33,41]. On the other hand, longer-term follow-up studies tend to report reduction of activity in anterior cingulate during the depressed state [4,9,22]. Time-of-day confounding may well play a role in these differences.

As discussed previously [13], an increase in "anergic depression" (see Table 1) was also associated with increased perfusion of cingulate cortex and associated limbic structures, such as the parahippocampal gyrus.
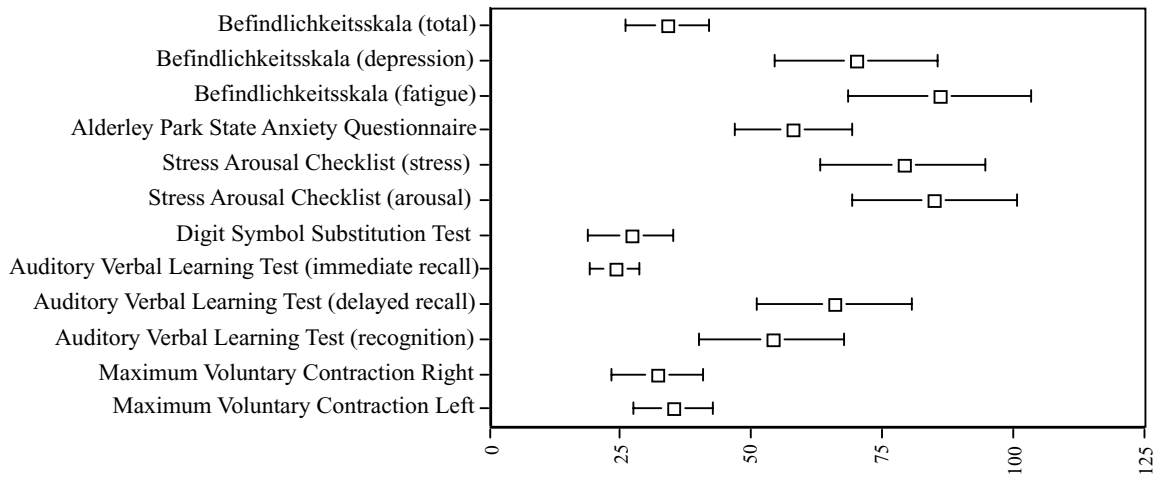
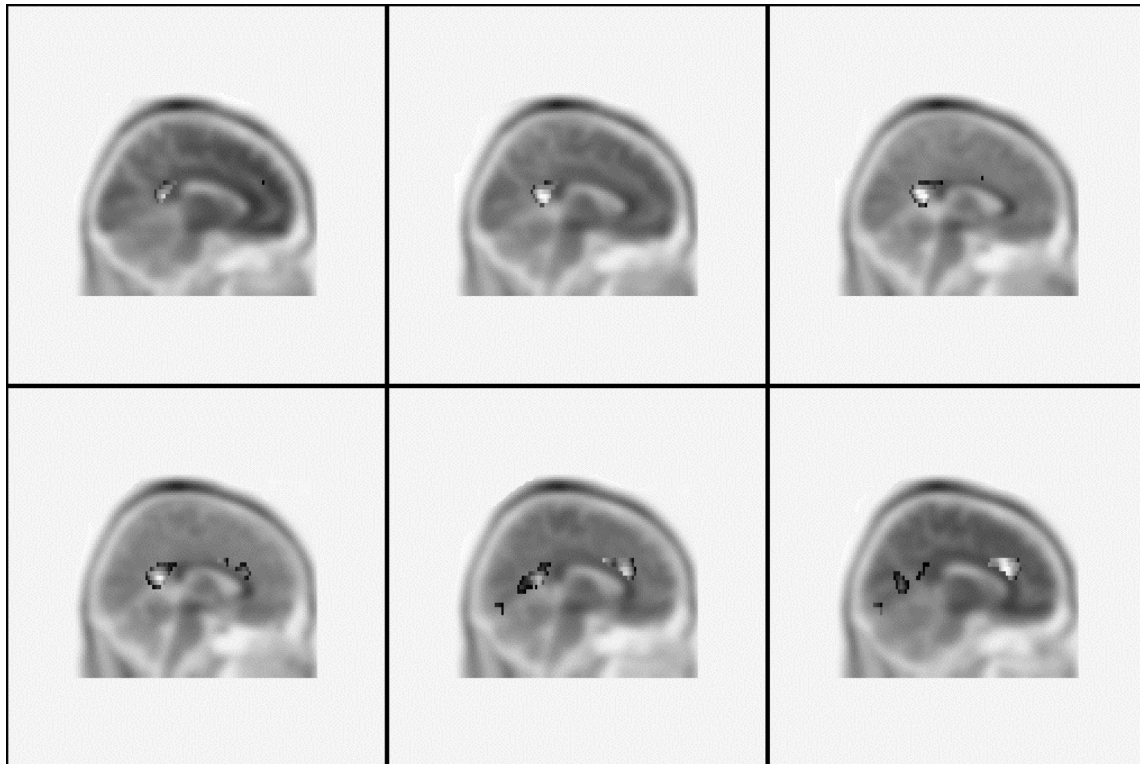Fig. 1. Absolute percentage changes for clinical and neuropsychological variables employed in the study.

Fig. 2. Sagittal slices from -10 to 10 mm (left to right of the midline) showing areas with significantly ($p < 0.01$) greater correlations between BFS and perfusion in the morning as compared with the evening scan.

5. Conclusion

It is tempting to speculate that as medial frontal structures are prominently innervated by dopaminergic projections from the ventral tegmental area, they may be responsible for changes in local neuronal activ-ity. Consistent with this notion, apomorphine infusions have been reported to result in medial frontal activation [17,21]. Psycho-motor retardation in depression has been found to be associated with increased binding to dopamine D2 receptors in basal ganglia, which suggests reduced activity in nigro-striatal dopaminer-

gic projections [11,12,37]. It is further tempting to speculate that at the nadir of depressed mood, i.e. usually first thing in the morning, compensating mechanisms should be the most active [30] – it will be remembered that even with a proportion of patients showing reversed diurnal patterns, some measures, such as maximum voluntary contraction and the DSST were most impaired in the morning. As pointed out earlier [9], it is not possible at this point to limit the underlying mechanisms to one single neurotransmitter, but testable hypotheses are required to increase our understanding of the mechanisms of depression.

6. Acknowledgements

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