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FDG-PET Study in Pathological Gamblers

1. Lithium Increases Orbitofrontal, Dorsolateral and Cingulate Metabolism

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Key Words
Pathological gambling · Relative glucose metabolic rate · Lithium · Orbital frontal cortex · Cingulate gyrus

Abstract
Background: Pathological gambling affects 1–3% of the adult population, and has high comorbidity. Although mood stabilizers and serotonin reuptake inhibitors have shown some efficacy in the treatment of this condition, there is little known about how these pharmacological interventions work. ***Methods:*** Twenty-one patients with pathological gambling, who met lifetime comorbid bipolar spectrum diagnoses, received baseline PET scans. Sixteen of these patients were entered into a randomized double-blind placebo-controlled parallel group design trial of lithium, and received follow-up PET scans at 10 weeks. A comparison group of 32 age- and sex-matched controls was also available. Anatomical MRIs were obtained as a structural template. ***Results:*** In patients with pathological gambling, relative glucose metabolic rates (rGMR) in the orbitofrontal cortex and medial frontal cortex were significantly increased at baseline compared to normal controls. Lithium increased rGMR further in the orbitofrontal cortex, heightening normal/patient differences, but it also increased the rGMR of the posterior cingulate and the dorsolateral frontal cortex normalizing the metabolic rate in these regions. ***Conclusion:*** Cortical areas implicated in impulse control disorders show increased rGMR in pathological gambling at baseline. Lithium treatment, while alleviating the symptoms, further increases rGMR in these areas.

Introduction

In a recent review article, Soares [1] noted that: 'in vivo brain correlates of treatment response with mood stabilizers have not yet been well characterized.' We are not aware of an FDG-PET study of the effect of lithium in patients with bipolar spectrum disorder or patients with pathological gambling. Functional imaging studies of the prefrontal cortex, however, especially the orbitofrontal cortex, have implicated dysfunction of these structures both in the bipolar spectrum and in pathological gambling. Brooks et al. [2] found increased orbitofrontal ('subgenual') activation in bipolar type I patients was associated with faster reaction times, but this correlation was absent in controls, suggesting orbitofrontal participation in fast reaction time response was abnormal and possibly associated with greater impulsivity. This was consistent with the findings of Drevets et al. [3], who also

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found the subgenual prefrontal cortex less active in depressed states in the bipolar spectrum. A recently published functional magnetic resonance imaging (fMRI) study reported that the healthy controls activated their ventromedial and subgenual prefrontal cortex during a 'loss-chasing game' more then during decisions to quit. The authors suggested that pathological gambling (PG) patients may have a neural substrate involving these areas, as loss-chasing is one of the cardinal symptoms of the disorder [4]. Compared to controls, patients with PG had greater activation of the prefrontal cortex Brodmann areas (BA) 9 and 44 while watching gambling-related images [5], lending evidence to the hypothesis that prefrontal cortex areas were also involved in craving aspects of pathological gambling.

The overlap of the bipolar spectrum and impulse disorders is also a prominent clinical phenomena [6]. Comorbidity represents a rule more then the exception in pathological gambling, and involves between 65 and 95% of the entire patient population. Among PG patients, bipolar disorder lifetime comorbidity has been rated from 9% [7] to 27% [8]; therefore, PG with a comorbid bipolar spectrum disorder represents a large part of the PG patients seeking treatment.

In our previous study, in an entirely different cohort of PG patients [9] assessed with FDG-PET, we found that monetary-rewarded blackjack was associated with a significantly higher relative metabolic rate in the primary visual cortex (BA 17), the cingulate gyrus (BA 24), the putamen, and prefrontal BA areas 47 and 10 compared to playing blackjack for points only. An fMRI study of the Iowa Gambling Task confirmed medial frontal/cingulate activation during decision-making and greater activation in gamblers than controls in ventral medial frontal areas [10]. This pattern, also observed in our previous cohort, suggests heightened limbic and sensory activation in gambling for monetary reward with increased emotional valence, and confirms the salience of monetary reward in pathological gambling. We therefore hypothesized that lithium effects would decrease relative metabolic rate in at least some portions of the cingulate and orbitofrontal systems. Since we have recently reported elevated relative white matter metabolic rates in frontal regions in patients with schizophrenia [11], and since the statistical parametric mapping analysis in fMRI gambling studies showed group difference clusters partially encompassing white matter underlying cortical areas [10], we assessed white matter metabolic rates underlying each BA on an exploratory basis.

In our previous treatment study, lithium was effective in reducing both gambling behavior and affective instability [12]. In the current study, we obtained FDG-PET from a subsample of those patients to examine the effect of lithium on brain metabolism and its relationship with the clinical outcome.

Materials and Methods

Subjects

Twenty-one patients with PG (14 men, 7 women; mean age = 44.42 years, SD = 8.57, range = 31–63) were recruited from the outpatient programs of Mount Sinai Medical Center and New York University. All of the subjects were evaluated with the Structured Clinical Interview for DSM-IV (SCID) and received a diagnosis of pathological gambling. A comorbid diagnosis within the bipolar disorder spectrum, including bipolar II (n = 6) or cyclothymia (n = 15) was also diagnosed. However, the patients did not meet criteria for a current episode of a mood disorder, which is in agreement with the DSM-IV diagnostic criteria, which does not allow a diagnosis of PG in the presence of a manic episode. Patients' total psychopathology scores on the Global Assessment of Functioning (SCID) ranged from 51 to 80 (mean = 66.29, SD = 7.95, median = 67.5), the Yale Brown Obsessive-Compulsive Scale scores adopted for pathological gambling (PG-YBOCS) [13] ranged from 13 to 36 (mean = 25.81, SD = 6.32, median = 24.50), and the South Oaks Gambling Screen scores ranged from 7 to 17 (mean = 12.47, SD = 3.34, median = 13.00). Sixteen of these patients entered to a double-blind randomized lithium treatment protocol. Eleven patients received placebo (8 with cyclothymia, 3 with bipolar disorder II) and 5 patients received lithium (4 with cyclothymia, and 1 with bipolar disorder II). All but 2 of the patients had had no previous psychopharmacologic treatment. The remaining 2 were prescribed benzodiazepines for anxiety, and were free from psychoactive medications for a minimum of 2 weeks. None of the patients were in psychotherapy, but 6 patients attended Gamblers' Anonymous meetings. All of the participants were screened by medical history, physical examination, and laboratory testing. After a complete description of the study, all participants provided written informed consent. These patients are a subsample of a larger psychopharmacological project [12]. Thirty-two normal controls, matched on age (means: men = 43.7 years, women = 42.8 years) and sex (22 men, 10 women) and scanned in exactly the same way, were available for comparison. The control subjects enrolled in a large trial studying the effects of normal aging on memory. They were assessed with Comprehensive Assessment of Symptom and History [14] semistructured interview to rule out axis I pathology. Control subjects were also screened for axis I pathology in their first-degree relatives. All the control subjects were at least high school graduates. Although the PG patients' IQ levels were not assessed, the controls were found to be within the normal IQ range by the Wechsler Memory Test [15].

PET (^{18}F)-Fluorodeoxyglucose Uptake Task and Procedure

Before the procedure, participants were read standard instructions about the serial verbal learning task (SVLT) [16], developed for the 32-min (^{18}F)-fluorodeoxyglucose (FDG)-uptake period,

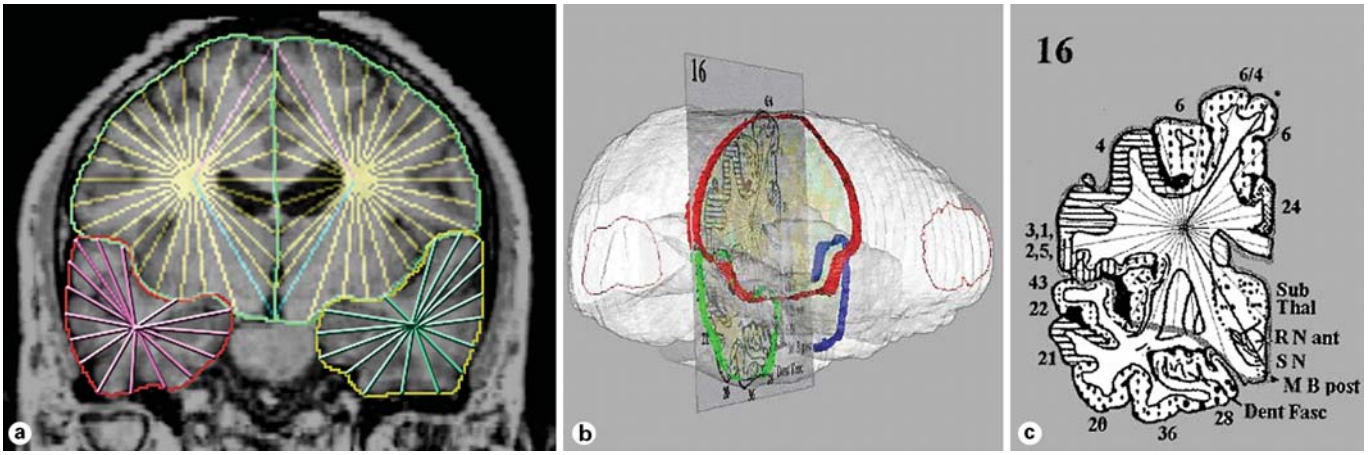

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Fig. 1. a Application of sectors to anatomical MRI. **b** Perry atlas in 3D position. **c** Perry atlas with BA identified.

which is analogous to the California Verbal Learning Test [17]. Scores were recorded for the total number of correctly recalled words, recall by semantic clustering, recall by serial ordering, intrusions (words not in the list), and perseverations (repetition of a correct word on the same trial). All patients were actively engaged in the SVLT task during FDG uptake. Patients with PG are not known to have impairments in working memory or semantic categorization. SVLT was employed as an uptake task to provide a controlled environment for subjects, as resting condition during FDG uptake is known to result in greater variability of the rGMR in cortical regions. The presence of a large well-screened control group scanned doing the same task was also an important factor.

PET and MRI Acquisition

PET scans (20 slices, 6.5-mm thickness) were obtained [18] with a head-dedicated GE scanner (model PC2048B) with measured resolution of 4.5 mm in plane (4.2–4.5 mm across 15 planes). T_1-weighted axial MRI scans were acquired with the GE Signa 5× system (repetition time = 24 ms, echo time = 5 ms, flip angle = 40°, slice thickness = 1.2 mm, pixel matrix = 2,565,256, field of view = 23 cm, total slices = 128).

PET and MRI Coregistration

The PET and MRI scans were obtained in the axial plane (canthomeatal line) through use of the same individually molded thermoplastic head holder. MRIs were resectioned to the standard Talairach-Tournoux [19] position. PET-MRI coregistration used the algorithm of Woods et al. [20]. Brain edges were visually traced on all MRI axial slices. Inter-tracer reliability on 27 individuals is 0.99 for area. For gray matter, white matter and cerebrospinal fluid (CSF) quantification, the coronal images are segmented into gray matter, white matter, and CSF using cutoff values individually determined in each subject by examining the within-brain-edge histogram of axial MRI values [21].

BA Measurements and Tissue Type Quantification

Perry method provided a coronal atlas (fig. 1), composed of 33 axial maps of BA, based on microscopic examination of entire hemisphere of a postmortem brain. Our earlier use of the Perry atlas [22–25] describes the method in greater detail. Coronal slices perpendicular to the anterior commissure/posterior commissure line were reconstructed in a 256 × 256 pixel matrix. First we determined the front (first slice containing the cortical ribbon) and back of the brain (last slice containing the cortical ribbon) and identified 33 evenly spaced slices such that the first slice began 1/34th of the distance from front to back. For each temporal lobe, we identified the temporal pole and the most posterior extent of the Sylvian fissure, and divided the space into 13 equally spaced slices. The brain edge was obtained on the approximately circular 33 nontemporal slices and 26 (13 in each hemisphere) temporal slices by depositing points visually on the tips of the gyri and then fitting a spline curve to the points. Each slice was then divided into 20 radial sectors on each hemisphere surface and 10 midline sectors [24]. BA were then assessed for the gray, white and CSF pixels within each sector (see segmentation method below); means are weighted according to the number of sectors in each region of interest and proportionately combined to obtain a single measure. Some of the smallest BA are combined (e.g. 3-1-2-5) for conservative simplicity. Data from 39 BA identified by Perry (1-2-3-5, 4, 6, 8, 9–12, 17–25, 27–32, 34–47, 7a and 7b) were obtained.

Reliability of the application of the Brodmann parcellation program to FDG-PET images has been tested with previous data sets with two PET scans (areas 11, 12, 17–19, 28, 34, 36, 38, 44–47 in each hemisphere). Significant positive correlations between the two scans were detected for all areas with a median intraclass test-retest correlation of 0.55.

Statistics

Because our hypotheses, based on the previous literature, focused on the orbitofrontal and anterior cingulate, we chose to use specific regions of interest in our analyses. We used repeated-measures MANCOVA and follow-up ANOVA to assess effects across groups of regions of interest in both hemispheres. This strategy evaluates both group differences and differential regional drug effects while minimizing the multiple testing type I errors associated with individual t tests on every brain area. For group differences, we entered normal and patient baseline data with di-

agnosis as an independent group dimension and brain areas as repeated area dimensions. Although there were no group differences in age, we used age and sex as continuous measures as our cohort consisted of subjects with a wide age range. For treatment effects we calculated the differences in rGMR (postmedication scan minus baseline scan) and entered the data into a 5-way analysis, with repeated measures on all dimensions which included medication (placebo, lithium), hemisphere (right, left) × frontal lobe division (anterior, medial, orbital, and dorsolateral) × BA within each region (anterior: BA 8, 9, 10; medial: BA 32, 25, 24; orbital: BA 11, 12, 47; and dorsolateral: BA 44, 45, 46) × matter type (gray, white). Age and sex were covariates in all analyses.

Results

Effect of Lithium

Behavioral Scores

We defined medication or placebo response in terms of the percentage change in total PG-YBOCS scores from baseline. As changes in PG-YBOCS scores are not commonly used for treatment response in PG patients, we used a 50% decrease from baseline as a threshold for responders. Four out of 5 patients (80%) who received lithium, and 3 out of 11 patients who received placebo (27%) met these strict criteria. The average PG-YBOCS 'total' and 'urge' percentage improvement scores were greater in the lithium group than the placebo group [60.5 ± 25.8 vs. 28.0 ± 30.0% (SD)], but this was significant only at a trend level (t = 2.21, d.f. = 14, p = 0.055). The SVLT yields 5 scores: number of correct words, number of intrusions, number of perseverations, semantic categorization and serial order. At baseline, patients were able to remember a fewer number of words than the controls (10.1 ± 2.3 vs. 12.8 ± 1.9, respectively, t = 4.8, d.f. = 51, p = 0.0001) and categorize them less (4.9 ± 2.3 vs. 7.6 ± 2.8, t = 3.7, d.f. = 51, p = 0.0005). There were no group differences in the number of intrusions or perseverations. There was no significant effect of lithium on the improvement in the SVLT subscores, as shown by independent t tests of the 2 groups.

Comparison between Normal and PG Groups at Baseline

We entered the relative metabolic rate for the BA of the prefrontal cortex region into a hemisphere × frontal lobe division (anterior, medial, orbital, and dorsolateral) × BA within each region (anterior: BA 8, 9, 10; medial: BA 32, 25, 24; orbital: BA 11, 12, 47; dorsolateral: BA 44, 45, 46) × matter type (gray, white) and age and sex as covariates. PG patients showed higher levels of activation in the gray matter relative to controls in the orbital lobe and the gray matter of BA 25, but lower levels of activation in the dorsolateral lobe of the prefrontal cortex. In white matter, gambling patients showed consistently higher levels of glucose metabolism as compared to controls as shown in a lobe division × BA × matter type MANCOVA (fig. 2; Wilks = 0.755, d.f. = 6, 44, p = 0.044).

Orbitofrontal Lobe at Baseline

We entered the BA that compose the orbital prefrontal cortex (BA 11, 12, 47) into a mixed-factorial MANCOVA, with age and sex as covariates. There was a significant effect of diagnosis on rGMR within the orbitofrontal lobe of the prefrontal cortex (F = 17.14, d.f. = 1, 49, p = 1.4×10^{-4}). PG patients showed significantly higher rates of glucose activation than normal controls during the SVLT task. In addition, a BA × diagnosis analysis almost reached significance (F = 2.96, d.f. = 2, 98, p = 0.056).

Lithium Effect. Both the white and gray matter showed activation with lithium as compared to the placebo treatment, particularly of the white matter within BA 11 and 12 in the left hemisphere (fig. 3; medication × hemisphere × BA × matter type; Wilks = 0.50, F = 5.49, d.f. = 2, 11, p = 0.022).

Dorsolateral Frontal Lobe at Baseline

At baseline, there was a significant interaction within the dorsolateral lobe of the prefrontal cortex as seen in a BA × matter type × diagnosis analysis (fig. 4; Wilks = 0.811, d.f. = 2, 48, p = 0.0065). PG patients showed decreased levels of glucose activity throughout the gray matter as compared to normal controls, but had either higher (BA 45) or similar rGMR (BA 44 and BA 46) activity in the white matter.

Lithium Effect. Lithium consistently activated BA 44 and 45 across hemisphere and matter type relative to baseline and placebo. Region 46, however, showed little change following either treatment. There was a significant lithium effect as observed in a treatment × BA × matter type interaction (fig. 5; Wilks = 0.540, F = 4.69, d.f. = 2, 11, p = 0.034) as well as a treatment × hemisphere × BA interaction (Wilks = 0.532, F = 4.84, d.f. = 2, 11, p = 0.031).

Medial Frontal Lobe at Baseline

PG patients showed significantly higher levels of glucose activation during the SVLT word task through all Brodmann regions of both hemispheres within the medial frontal lobe (fig. 6; hemisphere × BA × diagnosis; Wilks = 0.850, p = 0.020). Of the 3 regions, BA 25 showed the largest relative glucose levels in PG patients. The cingulate gyrus demonstrated lower levels of glucose activity in patients as compared to normal controls, with the ex-

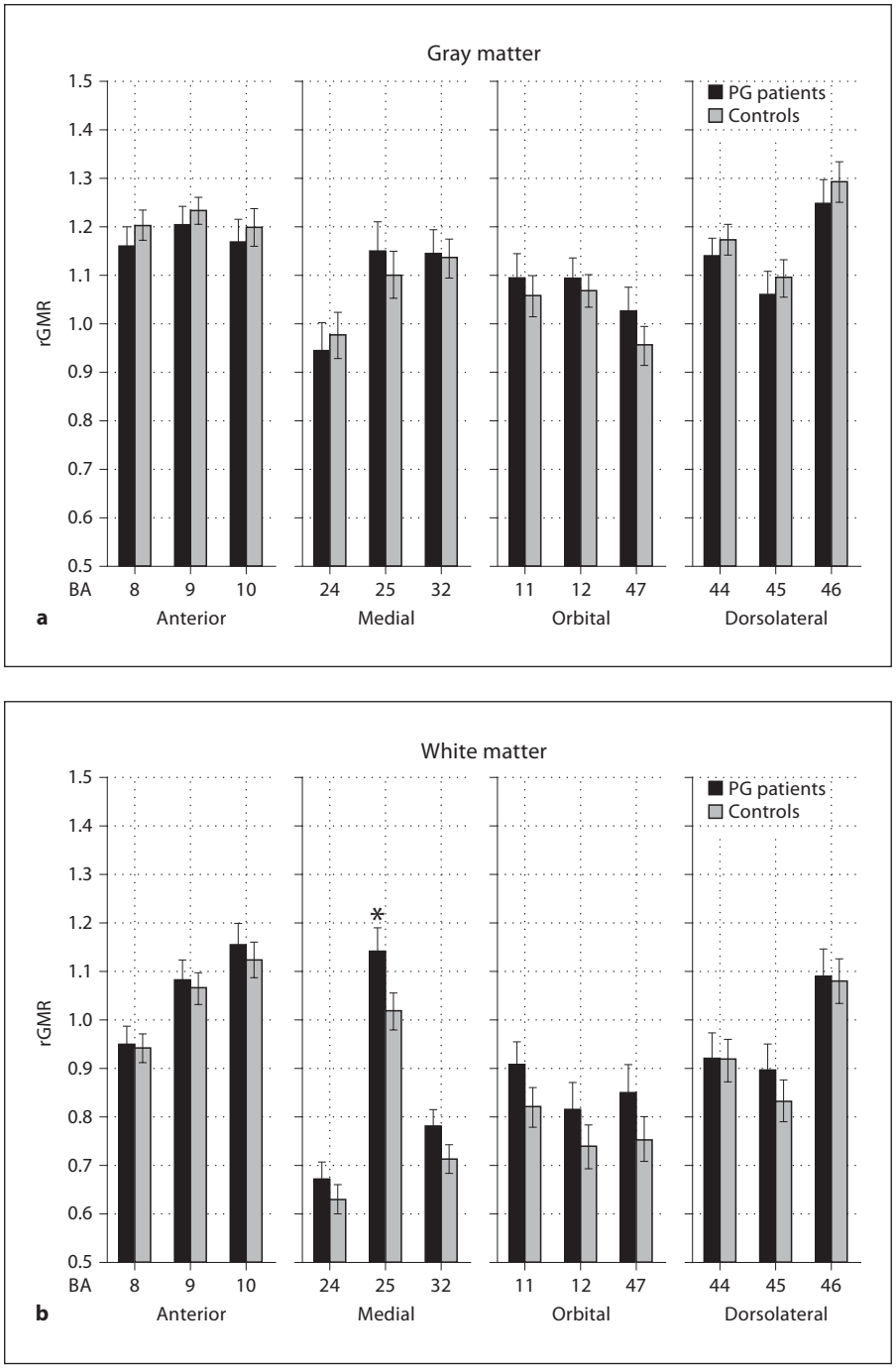
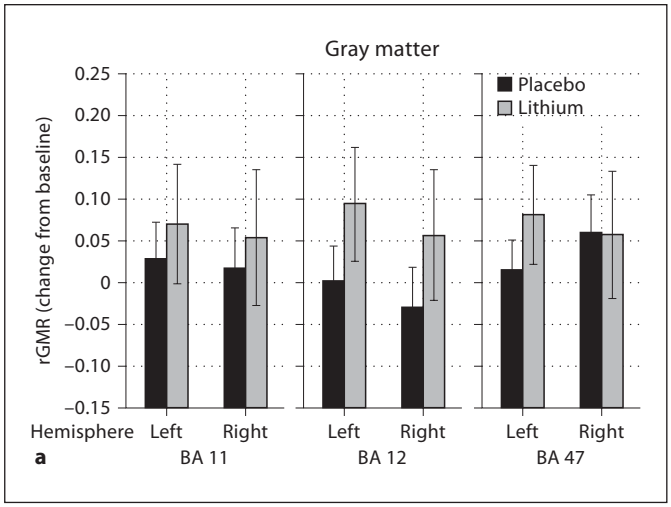
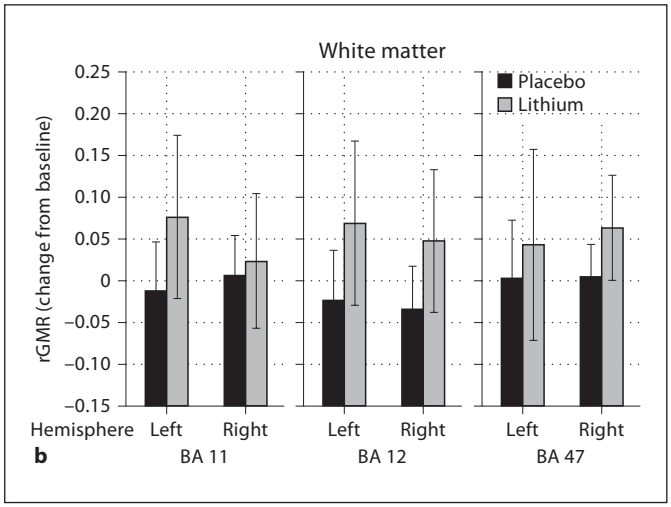


Fig. 2. Anterior-medial-orbital-dorsolateral × BA × matter type [gray (**a**), white (**b**)] × group analysis of baseline rGMR in frontal lobe areas. Medial and orbital frontal cortex activity increased in PG patients (Wilks: 0.755, F = 2.38, d.f. = 6, 44, p = 0.044). * $p < 0.05$, post hoc t test.

ception of BA 25 gray and white matter and the white matter of BA 24 (fig. 7; Wilks = 0.811, d.f. = 4, 46, p = 0.043).

Lithium Effect. There was no overall effect of lithium treatment in the medial prefrontal cortex. However, there was a significant effect of lithium treatment within the cingulate gyrus (BA 25, 24, 23, 31, 29) as demonstrated by a medication × BA interaction (fig. 8; Huynh-Feldt adjusted F = 3.01, d.f. = 3.52, 42.3, p = 0.034). Regions 25 and 29 show activation following treatment relative to baseline and to placebo treatment, whereas regions 24, 31, and 23 show deactivation relative to baseline and placebo.





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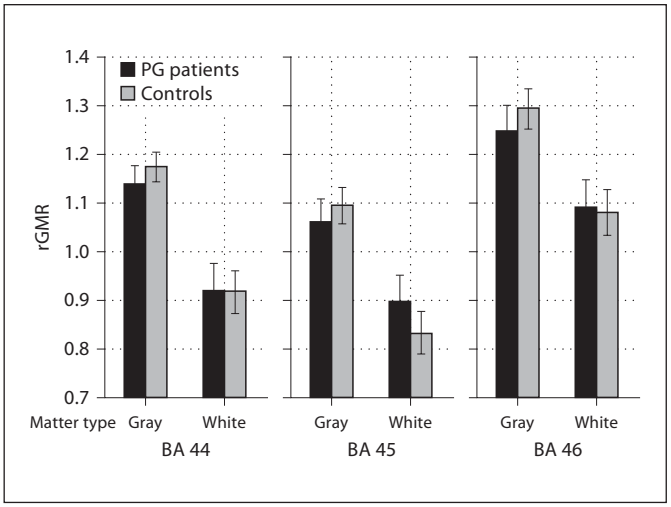

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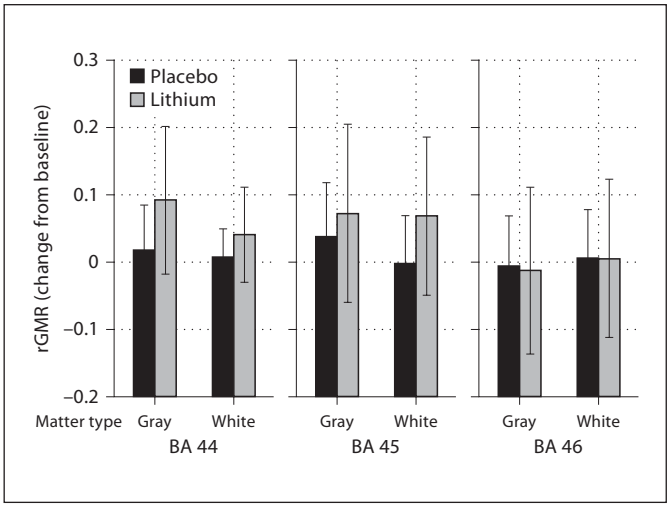

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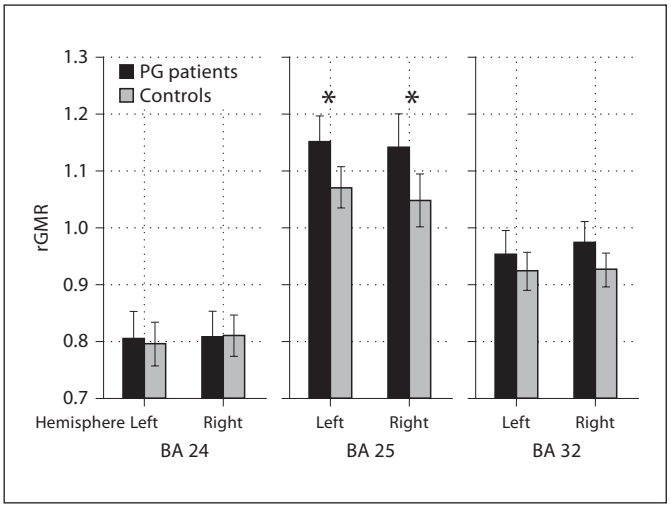

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Fig. 3. Medication × hemisphere × BA × matter type [gray (**a**), white (**b**)] analysis of lithium effect in orbital frontal cortex. Lithium increases rGMR both in white and gray matter (Wilks = 0.50, F = 5.49, d.f. = 2, 11, p = 0.022).

Fig. 4. BA × matter type × diagnosis analysis of dorsolateral frontal cortex rGMR at baseline. Gray matter rGMR is higher in control subjects (Wilks = 0.811, d.f. = 2, 48, p = 0.0065).

Fig. 5. BA × matter type × lithium/placebo analysis of the effect of lithium on the rGMR of the dorsolateral frontal cortex. Lithium increases the rGMR of BA 44 and BA 45 gray and white matter (Wilks = 0.540, F = 4.69, d.f. = 2, 11, p = 0.034).

Fig. 6. Hemisphere × BA × diagnosis analysis of medial prefrontal cortex rGMR at baseline. PG patients have increased rGMR in the subgenual cingulate cortex compared with control subjects (Wilks = 0.850, p = 0.020). * p < 0.05, post hoc t test.

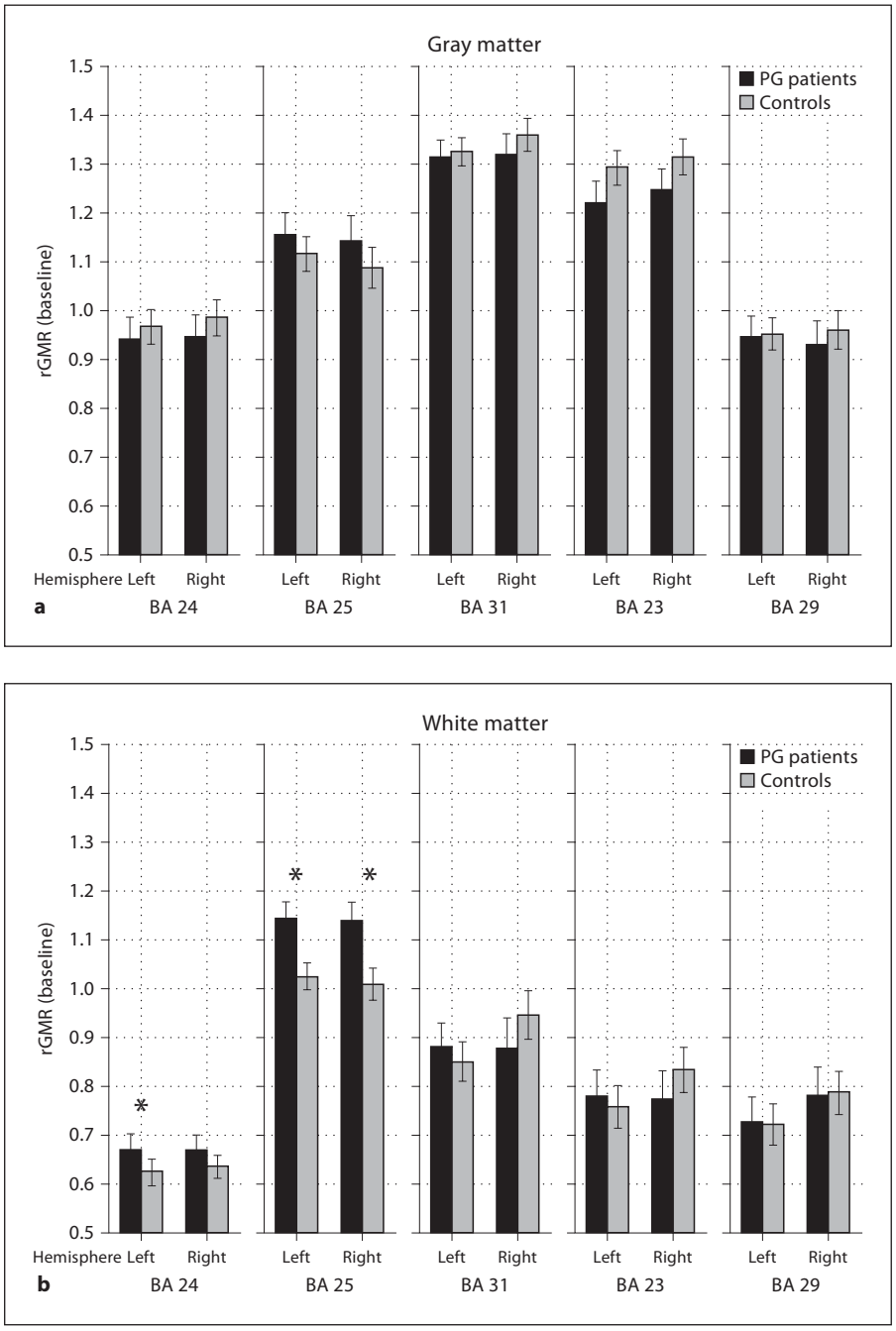

Fig. 7. Hemisphere × BA matter type [gray (**a**), white (**b**)] × diagnosis analysis of cingulate cortex rGMR at baseline. PG patients have increased rGMR of the subgenual anterior cingulate, most significantly in the white matter, while controls have an increased rGMR in the posterior cingulate cortex. * $p < 0.05$, post hoc t test.

Anterior Frontal Lobe at Baseline

Control subjects had higher rGMR in the gray matter of the entire anterior prefrontal cortex bilaterally (BA 8, 9, 10) as demonstrated by a matter type × diagnosis interaction (fig. 9; Wilks = 0.84, F = 9.42, d.f. = 1, 49, p = 0.0035). Lithium treatment had no effect on the rGMR of the anterior prefrontal cortex.

Treatment with lithium in PG patients tended to move the relative dorsolateral prefrontal cortex metabolic rate in the direction of normal controls, but further increased orbitofrontal metabolic rates. No statistical test of this effect is provided since normal controls were not tested twice, and all lithium data was obtained on a second scan.

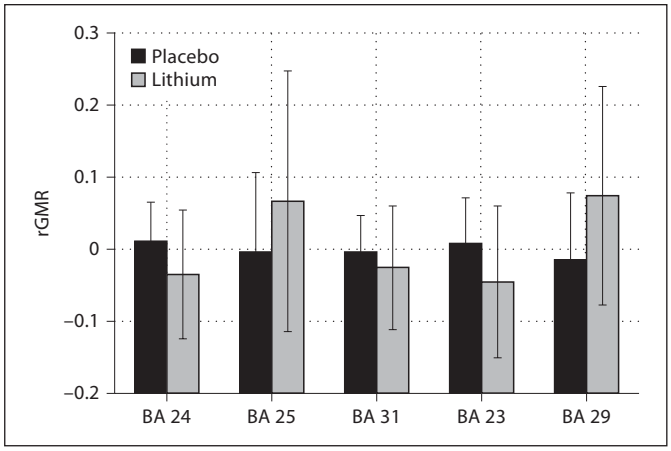

Fig. 8. Medication × BA analysis of the lithium effect on the cingulate cortex rGMR. Lithium increases the rGMR further in the subgenual anterior cingulate while lowering the rGMR in parts of the posterior cingulate (Huynh-Feldt adjusted F = 3.01, d.f. = 3.52, 42.3, p = 0.034).

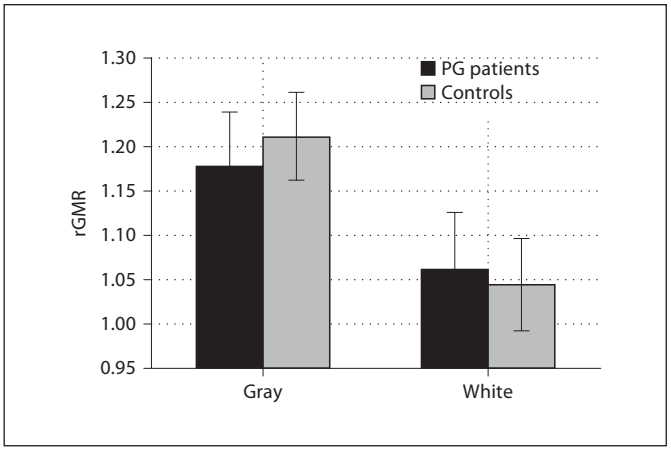

Fig. 9. Matter type × diagnosis interaction of the anterior prefrontal cortex rGMR at baseline. PG patients have reduced rGMR in the gray matter, while they show increased rGMR in the white matter of the anterior frontal cortex compared to controls (Wilks = 0.84, F = 9.42, d.f. = 1, 49, p = 0.0035).

Correlations with Clinical Change after Lithium

Because we observed a significant effect of lithium across the orbitofrontal cortex and right dorsolateral frontal cortex, we examined the correlation of relative metabolic change scores (week 10 scores – baseline scores) with change scores for the PG-YBOCS 'urge', 'behavior', and 'total' clinical measures on an exploratory basis. Significant correlations were seen with the improvement on the 'urge' scale throughout the gray matter of the prefrontal cortex, most particularly the left hemisphere of the anterior lobe and region 11 of the orbitofrontal lobe ($p < 0.05$; table 1). Increases in glucose activity within the total anterior lobe and total dorsolateral lobe were significantly correlated to improvements in the PG-YBOCS 'urge' measure. Improvements in 'behavior', with a reduction of the dysfunctional PG behavior, were correlated significantly with an increase in glucose activity (specifically in BA 8, left of the left hemisphere of the anterior lobe, and BA 11 of the orbital lobe; $p < 0.05$; table 1).

An increase in activity in white matter was significantly correlated to the 'total' PG-YBOCS score, as seen in BA 8 of the anterior lobe ($r = -0.89$, $p = 0.042$), and BA 47 of the orbitofrontal cortex ($r = -0.85$, $p = 0.068$). In addition, the white matter of the entire anterior lobe, as well as the complete dorsolateral lobe (gray and white), showed significant correlations of increased glucose activity with improvement on the 'urge' score ($r = -0.85$, $p = 0.071$; $r = -0.89$, $p = 0.043$; respectively).

Discussion

Gray Matter rGMR and Pathological Gambling

In comparison with normal volunteers, patients at baseline had higher activity in the orbitofrontal and subgenual anterior cingulate (BA 25), but lower activity in the dorsolateral prefrontal cortex. In a very oversimplified view, this is consistent with diminished balance between executive planning in dorsolateral cortex and emotional reactivity in the anterior inferior cingulate and orbitofrontal region. These areas correspond to prefrontal areas reported to be impaired in PG with neuropsychological tests [26, 27].

Increased metabolic activity in the orbitofrontal and medial prefrontal cortex in PG patients is different from results in other impulsive populations, such as borderline personality disorder [28], but is consistent with similar findings in OCD where elevated baseline metabolism has been interpreted as a good therapeutic predictor of response to serotoninergic treatments [29–31]. The unexpected outcome of the current study was that, although the lithium treatment has been clinically effective in reducing gambling behavior, it did not reduce metabolic hyperactivity and instead increased it further.

The baseline metabolic hyperactivity in the prefrontal cortex areas may also be interpreted as an expression of a mode of coping with functional impairment through the recruitment of an alternative neural network as a compensatory mechanism. However, the precise meaning of our

Table 1. Correlations of increases in prefrontal BA glucose activity in gray matter to improvements in YBOCS 'urge' and 'behavior' scores (negative correlation demonstrates improvement; * $p < 0.05$, ** $p < 0.01$)

BA	Urge	Behavior
Anterior lobe		
Left		
8	–0.94**	–0.91**
9	–0.82*	–0.64
10	–0.88**	–0.69
Right		
8	–0.73	–0.72
9	–0.69	–0.62
10	–0.86*	–0.62
Total	–0.98**	–0.83*
Orbital lobe		
Left		
11	–0.97**	–0.89**
12	–0.48	–0.47
47	–0.055	–0.09
Right		
11	–0.93**	–0.61
12	–0.22	0.029
47	–0.87*	–0.54
Total	–0.70	–0.51
Medial lobe		
Left		
32	–0.72	–0.57
25	–0.81*	–0.42
24	0.067	0.42
Right		
32	–0.85*	–0.64
25	0.13	0.63
24	0.16	–0.23
Total	–0.72	–0.29
Dorsolateral lobe		
Left		
44	–0.63	–0.19
45	–0.46	–0.10
46	–0.84*	–0.85*
Right		
44	–0.83*	–0.39
45	–0.90**	–0.43
46	–0.76	–0.34
Total	–0.90**	–0.43

findings requires an assessment of the rGMR of other areas that have not been analyzed in the present paper. In a more speculative manner, we may argue that since numerous reports show that lesions to the orbitofrontal cortex lead to choice deficits in various domains, and imaging studies indicate that the orbitofrontal cortex activates when people make economic choices [32, 33], BA 12 in particular could be involved in compensatory mechanisms resulting in a metabolic increase due to effective treatment.

Lithium Effects

Lithium administration was associated with widespread effects in the prefrontal cortex and cingulate gyrus. The rGMR in the orbitofrontal cortex, dorsolateral frontal cortex, subgenual cingulate cortex (BA 25) and posterior cingulate were significantly increased on lithium. This is not entirely dissimilar to the 6-week changes noted on fluoxetine with FDG-PET [34]. Increases in these areas were also seen in patients with autism treated with fluoxetine [35], but not in OCD, where clinical response has been reported as associated with a reduction of the activity [29–31]. It is of interest that BA 25 is a target area for deep brain stimulation treatment of depression and OCD [36], and was one of the regions that had a significant correlation with treatment response in our study. Lithium tended to normalize dorsolateral frontal cortex, but increase activity in the orbitofrontal cortex, heightening normal/patient differences. Dorsolateral frontal decreases were associated with Hamilton items on a factor reflecting loss of motivated behavior [37], while items loading on a psychiatric depression factor were associated with changes in the cingulate gyrus.

Cingulate Function in Inhibiting Irrelevant Information

Diminished performance on the Stroop test, a task well identified with the anterior cingulate in imaging studies, and indicating diminished ability to modulate irrelevant information, has been found in PG patients [38] and patients with attention deficit disorder [39]. Stroop activation deficits have been seen in patients with bipolar disorder [40], but differences were more prominent in posterior cingulate.

White Matter Differences

Patients with PG had greater white matter activity in the anterior cingulate BA 25 and orbitofrontal cortex (BA 11-12-47) than controls. It is of interest that changes in myelin staining decreases have been recently observed in frontal white matter in bipolar patients [41], but the mechanism of change is uncertain. The possibility of detecting repair or immune activity is suggested by the finding of cell adhesion molecule immunoreactivity, a possible marker of inflammation, in the anterior cingulate, and in greater quantities in white matter than gray [42]. The possibility that lithium may affect brain cytokines and that

their modulation may be important in antidepressant response is reviewed elsewhere [43] and cannot be excluded. Greater attention to white matter areas of the prefrontal cortex in functional imaging studies and the collection of imaging and immune measures on the same patients would be helpful in evaluating this speculation.

On lithium, right hemisphere area 47 tended to show greater rGMR increases in white matter than gray matter, suggesting changes in neural traffic, or tonic stimulation. It is unclear whether lithium could affect defective maintenance of oligodendroglia, incomplete axonal myelination or axonal loss, the factors suggested for the myelin-staining change, but this cannot be excluded. An interaction with the immune system, as noted above, is also a potential factor.

Study Limitations

Limitations of this study include the small sample size, presence of bipolar disorder comorbidity, and a FDG-PET task with the advantage of comparison groups, but not direct assessment of cognitive processes directly related to gambling. While the sample size is small, similar sample sizes are widely used in animal deoxyglucose studies of lithium effects [e.g. 44] with similar effect sizes. While the patients differed across the bipolar spectrum, they had in common the deficits associated with gambling and received uniform treatment. The serial verbal learning task involves short-term word list learning, a skill not entirely unrelated to certain gambling-related cognitive activity, but it does not assess impulsivity, risk-taking, or other hypothesized individual perceptual style aspects of gambling. However, the availability of a large sample of matched normal controls provided a normal baseline for understanding how the direction of lithium effects related to change. While we observed significant lithium effects in ANOVA encompassing multiple BA and both hemispheres, individual t tests were limited in power to support lithium effects. For example, BA 29 on the left showed a lithium effect size of 0.92, which has power of 0.38 to detect a 0.05 effect. This power limitation suggests that lithium effects in some cortical areas may not have been detected at the $p < 0.05$ level. We did not observe lithium toxicity in this trial. Interestingly, SPECT findings in lithium toxicity appear to include decreases in parietal flow [45], a finding which did not appear in our data. Since PG, as categorized in DSM IV-TR, does not have distinguishable subtypes, PG with bipolar disorder lifetime comorbidity have to be considered as PG. We added comorbid conditions as descriptive futures of our patient population. Therefore, PG with bipolar lifetime comorbidity is representative of a large clinical subpopulation, but is probably neurobiologically distinguishable from other PG subpopulations characterized by different comorbidity. Further studies should be undertaken with PG patients without the bipolar disorder comorbidity to examine distinct neurophysiological patterns of pathological gambling.

Summary

We report that in PG patients at baseline the rGMR has increased in the orbitofrontal and medial prefrontal cortex. In a subsample of patients, who were randomized to placebo and lithium treatment, the lithium group showed further increases in the metabolic rate in prefrontal cortex areas. Patients who received lithium showed clinical improvement after 8 weeks. Taken together, these results suggest some similarities of lithium action and selective serotonin reuptake inhibitors. However, in contrast to patients who respond to selective serotonin reuptake inhibitors and show normalized rGMRs, in PG patients who are lithium responders the rGMR increased in the prefrontal cortex. Detailed study of the limbic system on the traced cingulate gyrus and amygdala and exploration of the striatum and globus pallidus will be important further steps in understanding the effect of lithium, and to explore the pathophysiology of PG in relationship to both bipolar and obsessive-compulsive spectrum disorders.

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