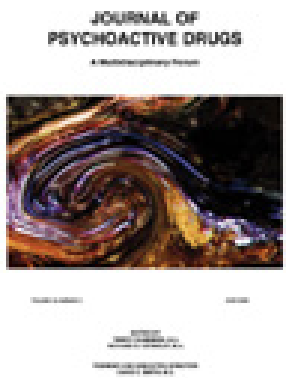

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Predicting Positive and Negative Treatment Responses to Stimulants with Brain SPECT Imaging†

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Abstract—The goal of this study was to test whether clinician-rated regional cerebral blood flow (rCBF) as rendered by SPECT imaging is a meaningful predictor of patient response to CNS stimulants. Chart reviews were used to identify patients who reported prior significant positive and negative responses to CNS stimulants. Each patient in the study had received resting and concentration SPECT scans using Tc99m exametazime. Differences in cerebral blood flow for frontal regions of interest were assessed in three conditions (resting, concentration, and their difference, or "delta") using ANCOVAs and age-matched ANOVAs. Prefrontal pole deltas were found to be highly sensitive and specific predictors of response to CNS stimulants, with pole activation predicting adverse responses and pole deactivation predicting good responses. Positive and negative predictive values were greater than .75 for both poles. We conclude that SPECT renderings of rCBF, particularly in the prefrontal cortex, are a potentially powerful clinical tool for anticipating response to stimulant medications, both positive and adverse.

Keywords—ADHD, CNS stimulant, neuroimaging, SPECT, treatment response

Clinical research has found central nervous system (CNS) stimulants to be helpful in treating many psychiatric disorders (Kajs-Wyllie 2002) such as depression (Morris et al. 1993; Koenig et al. 1989), narcolepsy (Kittur & Hauser 1999), and dementia (Goforth et al. 2004), as well as fatigue (Bruera et al. 2003), and they may also aid people who have experienced traumatic brain injury (Gualtieri & Evans 1988). At present, CNS stimulants are most commonly prescribed in the treatment of attention deficit/hyperactivity disorder (ADHD).

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ADHD affects between 3% and 11% of children under age eighteen (Shafritz et al. 2004; Wolraich et al. 1996), and about half that rate in adults (Santosh & Taylor 2000). In the majority of cases that get medically diagnosed, the first course of treatment is a CNS stimulant, as their effectiveness has been well documented (Murphy & Barkley 1996). More importantly, as catecholamine modulators they may treat the specific etiology of ADHD in that they stimulate brains whose prefrontal cortices (PFCs) are thought to be hypofunctional (Todd & Botteron 2001). Given the PFC role in executive function, impulse control (Spinella 2004), and directing attention (Pollman 2004), regulating dopaminergic transmission in this brain region is thought to be one of the factors mitigating ADHD symptoms in patients who experience a positive response.

In a number of ADHD trials, stimulants have been reported to have a positive response rate of about 65% (Shafritz et al. 2004; Biederman et al. 2003; Greenhill et

al. 2002). However, adverse events such as tics, insomnia and loss of appetite are not uncommon (Biederman et al. 2003; Greenhill et al. 2002) and tend to be similar for different stimulants (Cherland & Fitzpatrick 1999; Jadad et al. 1999). Additional research has found that adverse events can be extreme (Rothman et al. 2000), and in our patient histories adverse events have also been found to be severe in many cases: patients have reported hallucinations, violent outbursts, volatile temperament, psychosis, and suicidal ideations. Compounding these events is the fact that CNS stimulants are subject to abuse (Rothman et al. 2000).

Given the disparate disorders for which stimulants are prescribed and the significant subclass of patients who have a severe negative response, it would be helpful to have a sensitive, specific tool for assessing good and bad candidates for stimulant medication. Our goal was to determine whether adverse events could be predicted using single photon emission computed tomography (SPECT) brain imaging in a clinical setting. Previous studies have found SPECT useful in predicting treatment response. Using [123I]beta-CIT tropane-2beta-corboxylate, Kugaya and colleagues (2004) were able to correlate serotonin transporter availability in the diencephalon to positive SSRI response in depressed patients. Additionally, brain SPECT has been shown to predict response to cholinesterase inhibitors in Alzheimer's disease (Mega et al. 2000), to antidepressants (Navarro et al. 2004) and transcranial magnetic stimulation (Conca et al. 2000) in severe depression, and to mood stabilizers in bipolar disorder (Post et al. 2003).

Using extensive chart reviews of medical histories, we identified two groups of patients: those reporting a "significant positive response" to CNS stimulants, and those reporting a "significant negative response" as we define in our methods below. Each patient in the study received two SPECT scans, one performed at quiet rest and one performed during a computerized concentration task. This enabled us to compare response groups in three conditions: at baseline, during concentration, and the difference or "delta" (i.e., activation during concentration relative to baseline).

We hypothesized that the average regional cerebral blood perfusion (rCBF) would be significantly greater in the negative response group in frontal cortical areas relative to the rest of the brain as measured by SPECT. Our rationale was that relatively well-perfused frontal lobes would not require stimulation, and thus medicating them with stimulants might result in negative responses. Likewise, we supposed that hypo- or asymmetrically-perfused cortices might require stimulation and thus respond more favorably.

We also hypothesized that the negative response group would contain a higher proportion of brains with significant frontal activations during concentration than the positive response group. Our rationale was that activation during concentration was an indication of attentional resource allocation (Shaywitz, Fletcher & Shaywitz 1994), and thus brains that were allocating resources likely did not require stimulation, which, again, might induce a negative response. Additionally, we anticipated that the positive response group would contain a higher proportion of brains with significant frontal deactivations during concentration, as deactivation was a likely indication of suboptimal resource allocation.

METHODS

Subject Sample

We conducted an exhaustive review of 2,500 medical charts randomly selected from a large outpatient psychiatric clinic that specializes in brain imaging. The following criteria had to be met for a patient to be included in the study. First, the medication history had to clearly indicate the patient had taken a CNS stimulant under medical supervision prior to coming to the clinic for a diagnosis of ADHD and prior to any imaging information. No distinction was made between brand and generic forms. Second, the medication history had to contain a clear description of the stimulant response as either directly mitigating or exacerbating the ADHD diagnosis for which the patient was prescribed a stimulant. The patients' use of stimulants was confirmed with a telephone follow-up by a clinician who, without priming, asked patients to describe their responses and experiences. Third, the patient had to be right handed. Fourth, the patient must have been off stimulants for at least four days prior to the scan. Fifth, the patient must have received both a baseline and concentration scan, with images having been acquired within seven days of each other.

Three raters evaluated responses to stimulants along two dimensions: change in symptoms/condition as a result of stimulants, and reactions/side-effects to stimulants. Raters then used these two dimensions to categorize patients into three groups: "Significantly worse," where either a patient's ADHD symptoms were exacerbated or a patient had marginal or no improvement in ADHD symptoms AND had to discontinue use due to adverse events; "significantly better," where a patient's ADHD symptoms improved AND patient experienced no adverse events; and "benign," where patients report no change in symptoms nor any side effects. The following guidelines were used.

First, each patient was classified as significantly worse if any severe pathophysiological symptoms were reported as a result of stimulants (e.g., "I became psychotic," "I started hallucinating," etc.). A patient was also classified as significantly worse if side effects forced her to discontinue use of the medication in spite of marginal symptomatic improvement (e.g., "It helped me to concentrate at first, but I wanted to kill myself," "My grades improved, but I became prone to violent outbursts," etc.). Second, a patient was classified as significantly better if she reported dramatic improvement in conditions with no negative side effects (e.g., "My focus improved," "Our son can finally sit still," etc.). A patient was also classified as significantly better if she reported mild negative side effects but also reported dramatic improvement

TABLE 1
Characteristics of Patient Sample

	PosRx (N = 61)	NegRx (N = 96)	Group Totals	
Gender	45 male, 16 female	67 male, 29 female	112, 45	$p = .59$*
Age	23.8 years (SD = 16.7)	21.1 years (SD = 13.7)		$p = .28$**
Meeting DSM-IV Criteria, Based on Structured Interviews and Psychiatrist Evaluation at the Outpatient Clinic, After They Had Tried Stimulants:				
ADHD				
Inattentive Only	24	38	62	
Hyperactive Only	3	2	5	
Combined Type	15	36	51	
ADHD Totals	42	76	118	$p = .30$*
Depression	21	34	55	$p = .65$*
Bipolar Disorder	15	25	40	$p = .78$*
PTSD	5	9	14	$p = .69$*

*Significance based on pooled ttest.
**Significance based on Cochran-Mantel-Haenszel measure of general association.

and continued on the medication (e.g., "It's really helped my ability to concentrate, but I'm constantly urinating," etc.). A patient was classified as benign if she clearly derived no benefit and reported no adverse events. Three raters reached clear, blinded consensus on 96 charts classified as significantly worse, 61 charts classified as significantly better, and 36 charts classified as benign. This process yielded 96 patients who reported negative responses (NegRx group) and 61 patients who reported positive responses (PosRx group). The total sample thus consisted of 157 patients who had both a baseline and concentration scan. All patients in the study gave informed consent to have their anonymous data used in future research at the time of their initial visit to the clinic. All raters were blinded to any patient information other than that pertaining to their response. A description of between-group differences is given in Table 1.

SPECT Image Acquisition, Rendering, and Rating of ROIs

We used brain SPECT to capture functional images of regional cerebral perfusion as a surrogate for brain activity. In each study an age- and weight-appropriate dose of technetium Tc99m exametazime (commercially available as Ceretec®) was administered intravenously. Photon emission was captured using a high resolution Picker (Phillips) Prism 3000 triple-headed gamma camera with fan beam collimators. Data were acquired in 128x128 matrices, yielding 120 images per scan with each image separated by three degrees spanning 360 degrees. The data were prefiltered using a low pass filter with a high cutoff. Attenuation correction was performed using linear methods (Chang 0 homogeneous correction).

All images were processed using Odyssey software, with transaxial slices oriented horizontal to the AC-PC line. Coronal, sagittal, and transaxial slice images (6.6mm apart, unsmoothed) were then rendered in the Odyssey step-20 scale, which scales all voxels to the brain maximum and assigns each a color gradient based on its percentile of activity (see Figure 1). Each color step represents a (not necessarily linear) five-percentile-point change in rCBF.

Baseline images were acquired in the following manner. Patients sat upright in a quiet, dimly lit room with open eyes, and the bolus was injected after ten minutes. Patients sat for an additional ten minutes post-injection. Concentration images were acquired during a common 15-minute computerized task, Connors's Continuous Performance Test (CPT), again with the patient upright in the same light as in the baseline condition. The injection was administered three minutes into the CPT.

The following PFC regions of interest (ROIs) were visually inspected and rated in coronal, saggital, and transaxial slices by two clinicians trained in neuroanatomy using the Mai Atlas of the Human Brain (Mai, Assheur & Paxinos 1997): the left and right poles (medial aspect of Brodmann area 10, anterior rostral aspect of Brodmann area 12); the left and right inferior orbits (Brodmann area 11); the left and right anterior-lateral PFC (comprised of Brodmann areas 9, 11, 45, 46, 47, and the lateral aspect of area 10); the left and right mid-lateral PFC (comprised of Brodmann areas 6, 8, and 44); and the left and right posterior frontal region (comprised of Brodmann areas 1,2,3,4, and 43). The following semiquantitative rating scheme was used to rate rCBF: Activity rated above the 95th percentile was assigned a score of 4+; 91-95th was scored 3+; 86-90th was scored 2+; 81-85th was scored 1+; 61-80th was scored 0; 56-60th was scored –1; 51-55th was scored –2; 46-50th was scored –3; and 41-45th was scored –4. Because of the nonuniform nature of perfusion within any given ROI, each area was rated for its highest and lowest activity, and the average of the two was taken as a given ROI's final score.

When rating ROIs, raters were blinded to all patient information including their medication history. Interrater

FIGURE 1
Sagittal Slices of SPECT Images Showing Differences in Left Inferior Orbital Cortex

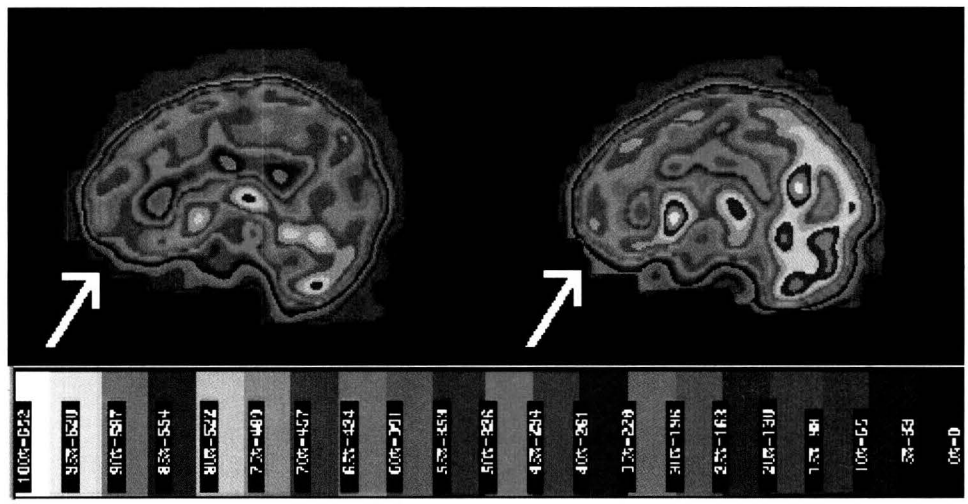
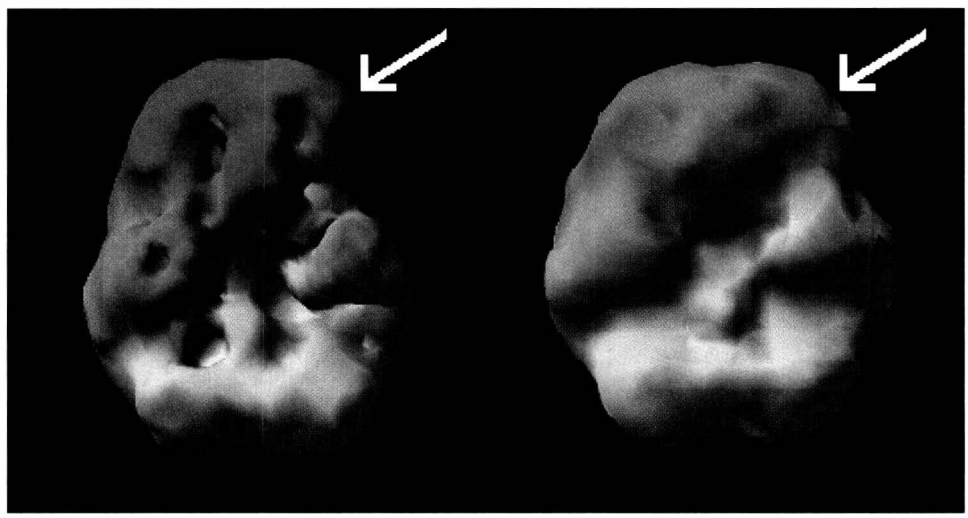


FIGURE 2
Inferior Surface SPECT Images Showing Activity at or Above the 55th Percentile Threshold



reliability was assessed using Cohen's Kappa, and coefficients were at .79 or above for all ROIs.

Figures 1 and 2 give an abbreviated example of how slices are used to rate rCBF. Figure 1 presents sagittal SPECT slices showing left inferior orbit perfusion in two subjects. Subject 1 (left) is a 31-year-old male patient presenting with ADHD and anxiety. Note the dark purple area indicating perfusion falling between the 56th and 60th percentile, for a rating of -3. Subject 2 is a 32-year-old healthy male control whose perfusion in this same area is pink, indicating activity between the 66th and 70th percentile, for a rating of 0. The thin outer red layer (46th-50th percentile) in both scans represents tracer uptake into cerebrospinal fluid. However, note that in Subject 1 the red is just beginning to encroach into the cortex, indicating a perfusion deficit, while in Subject 2 the red cleanly traces out the brain's anatomy, indicating fuller cortical activity.

Region-specific cortical perfusion was further explored using three-dimensional reconstructions wherein the image software fills in voxels whose activity is above some

arbitrary percentile of activity. Figure 2 shows the same two patients from Figure 1 using an activity threshold of the 55th percentile.

Subject 1's scan shows a number of areas where voxels do not fill in at the 55th percentile, most notably in the right and left orbital cortices, the anterior right temporal pole, and the left frontotemporal cortex. This is in contrast with Subject 2, where most activity falls above the threshold. These analyses were performed on each scan, and the activity threshold was manipulated to pinpoint the level at which perfusion deficits "fill in," allowing the clinician to fine-tune her region-specific ratings.

Statistical Analyses

To test between-group differences in rated rCBF while controlling for patient ages, we performed analyses of covariance (ANCOVAs). In lieu of t-tests, we used treatment response as our predictor variable and ROI rating as our criterion variable, including age and the group-age interaction as model covariates. We then made inferences based on partial sums of squares, which generates F-statistics and *p*-values controlling for covariates (in this case, age).

Because age was significantly correlated with all ROIs ($p < .0001$), additional analyses of variance (ANOVAs) were conducted on age-matched samples using an iterative, randomized resampling algorithm written in Statistical Analysis Software (SAS) 8.2, done in the following manner: Age frequencies were determined within both NegRx and PosRx groups. For any given age, the smaller group frequency was then taken as the number of patients to be sampled from within the group with the larger frequency. For example, if the NegRx group contained n 10-year-olds and the PosRx group had n+5 10-year-olds, n 10-year-olds would be randomly sampled from within the PosRx group and compared to the NegRx group. This procedure was done across all ages for each ANOVA iteration. After 1,500 iterations, we calculated an average of the resulting *p*-values and their standard errors, and then tested their distributions for non-normality using the Shapiro-Wilk W-statistic. Aside from controlling for age, no significant difference was found to exist between the groups (see Table 1), so we restricted our analyses to main effects.

To assess individual ROIs as predictors, we generated cross-tablulations and calculated sensitivity, specificity, and predictive values. Inferences were based on the Cochran-Mantel-Hantzel measure of general association test statistic. All of the above analyses were done in SAS 8.2.

RESULTS

For our randomly resampled age-matched ANOVAs the distribution of *p*-values of each ROI was found to be normal (Shapiro-Wilk W prob. > 05). All 1,500 runs had equal group sizes of 44 (88 subjects per two-group run), with mean ages of 18.2 years (SD = 12.2, min = 5, max = 56).

In attempting to discriminate between PosRx and NegRx groups, ANCOVAs identified five brain regions whose rCBF differences were at or approaching statistical significance, all in the concentration condition: the PosRx group had relatively lower rCBF in the left ($p = .05$) and right ($p = .06$) poles and left ($p = .06$) and right ($p = .10$) posterior frontal areas, and higher rCBF in the right mid-lateral PFC ($p = .06$). In our age-matched resampling analyses, only the mean *p*-values in the left ($p = .06$, SE = .06) and right poles ($p = .07$, SE . =.07) approached significance in the concentration condition. No significant difference between the two groups was noted at baseline.

Looking at the mean rCBF in both groups, we noted that prefrontal pole activity was approximately .13 rating points higher in the PosRx group at baseline, and that this relationship became inverted during concentration, with the PosRx group now approximately -.16 rating points lower. This suggested that considering both scans simultaneously might allow us to differentiate between positive and negative response groups. We thus calculated the difference between conditions by subtracting each patient's baseline rCBF ratings from her concentration ratings. The resulting delta values are positive when a given patient's ROIs are activated at concentration relative to baseline; likewise, they are negative when ROIs are deactivated at concentration relative to baseline.

We tested for between-group delta differences in the same manner as above, conducting ANCOVAs with age as a covariate, and running 1,500 randomly resampled age-matched ANOVAs. The results are reported in Table 2.

Here we note that the left and right pole deltas are significantly different between groups, and also that the sign of the PosRx mean is negative (i.e., *less* active during concentration) while the sign of the NegRx mean is positive (i.e., *more* active during concentration). This result appears robust, as it is supported in both analyses. Of the 10 candidate ROIs in this analysis, the left and right poles considered in both baseline and concentration conditions emerge as candidates for predicting treatment response.

To test the sensitivity and specificity of these two ROIs in predicting negative response to stimulants, we categorized delta values into three classes: "deactivation," "no change," and "activation." For an ROI delta to be categorized as deactivation, the concentration rCBF had to be rated at least 5% lower than at baseline (recall that 5% is one full color gradient in the Odyssey Step 20 Scale). For a delta to be considered an activation, the concentration rCBF had to be rated at least 5% higher. Two scans with an ROI rating falling within 5% of each other were considered "no change" for that ROI. We then cross-tabulated pole activations against stimulant response. Figure 3 shows these results for the left and right poles, respectively.

Left pole activations had positive and negative predictive values of .76 and .80 respectively, correctly classifying treatment response (both positive and negative) in 28 of 36

TABLE 2

Results of Age-Controlled ANCOVAs and Resampled ANOVAs Using Reaction to Stimulants to Predict Difference in rCBF Deltas (Delta = Concentration minus Baseline)*

	ANCOVAs						Resampling		
	PosRx Delta LS Mean	NegRx Delta LS Mean	Diff. (PosRx minus NegRx)	Type** III F-Value	Type III *p*-Value	Mean of *p*-values (SE)	PosRx Mean (SD)	NegRx Mean (SD)	(PosRx minus NegRx)
ROI Delta (Conc. Minus Base.)									
Left Pole	-0.11	0.17	-0.28	6.09	***0.01***	***0.03*** (.03)	-0.10 (.10)	0.23 (.10)	***-.33***
Right Pole	-0.10	0.19	-0.29	7.32	***0.01***	***0.04*** (.04)	-0.07 (.11)	0.28 (.10)	***-.35***
Left Orbit	-0.10	0.08	-0.18	0.06	0.81	0.70 (.22)	-0.05 (.17)	0.01 (.16)	-.06
Right Orbit	0.29	0.26	0.03	0.78	0.38	0.70 (.21)	0.38 (.14)	0.36 (.14)	.02
Left AntLatPFC	0.17	0.25	-0.08	0.82	0.37	0.50 (.26)	0.13 (.14)	0.27 (.14)	-.14
Right AntLatPFC	0.24	0.09	0.15	0.44	0.51	0.63 (.23)	0.16 (.15)	0.08 (.15)	.08
Left MidLatPFC	0.03	0.13	-0.10	0.32	0.57	0.59 (.24)	0.03 (.15)	0.13 (.15)	-.10
Right MidLatPFC	0.12	-0.10	0.22	0.78	0.38	0.40 (.23)	0.09 (.19)	-0.15 (.19)	.24
Left Posterior Frontal	-0.05	0.10	-0.15	0.01	0.94	0.68 (.21)	-0.02 (.10)	0.01 (.10)	-.03
Right Posterior Frontal	0.05	0.15	-0.10	1.18	0.28	0.74 (.18)	0.06 (.13)	0.06 (.12)	.0

* *p*-values uncorrected for multiple comparisons.

**Main effect for age significant at $p < .01$

cases. Similarly, right pole activation had positive and negative predictive values of .78 and .79 respectively, correctly classifying treatment response in 29 of 37 cases.

DISCUSSION

This study set out to test two hypotheses: whether clinician-rated frontal rCBF and clinician-rated activations could predict a negative response to stimulants *post hoc*. Regarding the first, we found little evidence to suggest that any single frontal ROI is predictive. We did see five ROIs approach statistical significance at concentration, four of which showed higher rCBF in the negative response group in support of our hypothesis. While interesting, however, these results lacked robustness.

Regarding our second hypothesis, we found strong support for clinical SPECT in predicting treatment response, albeit ex post facto. Using pole activation as the only criterion, clinician-rated SPECT was highly sensitive (.84 on the left; .86 on the right) and also highly specific: Deactivation accurately classified positive responses seven of ten times.

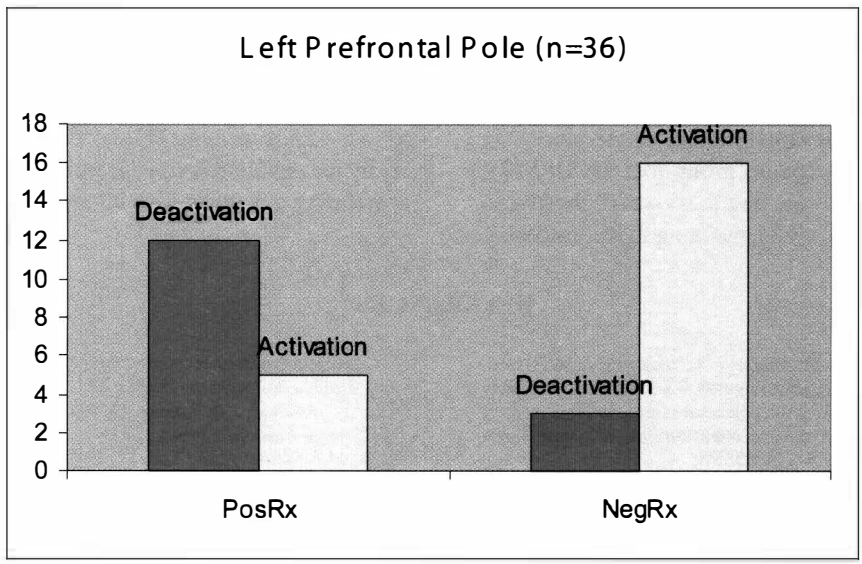
It is interesting to note that we would have found this same result if both response groups activated during concentration so long as the between-group difference in mean activation remained similar. However, the fact that the mean delta signs in each group were inverted is highly suggestive of differences in functional typology, in particular, the capacity allocation model proffered by Shaywitz and others (Fletcher, Shaywitz & Shaywitz 1994; Shaywitz, Fletcher & Shaywitz 1994). Prefrontal pole activation may indicate the brain's ability to allocate attentional resources, as some brains appear to be shutting down these resources when forced to concentrate: It is these brains that seem to do well on CNS stimulants. Brains that allocate attentional resources ostensibly do not.

Also interesting is that the relationship between pole activation and response appears to hold irrespective of age in this sample. This result is particularly important given recent genetics work by Shaw and colleagues (2007). Their longitudinal study found that ADHD children with a polymorphism on the dopamine D4 receptor (DRD4 7-repeat allele) also showed thin neocortical layers during preadolescent stages of neural development. Shaw also found this phenomenon ultimately corrected itself in post-adolescent development, suggesting this allele as a marker for predicting a clinical resolution of symptoms. The present results compliment Shaw's work in suggesting functional images may be used to predict a positive response to stimulant medication—possibly in cases where clinical symptoms would persist. Further research that combines these genetic, anatomical, and functional aspects of predicting clinical outcomes is clearly warranted.

There are several limitations to this study. First, all data were collected retrospectively from patient charts. We were therefore unable to control for potential confounds such as the length of time patients were on stimulants, dosages, and myriad other factors that might affect the outcome. Further, the measure of our criterion variable (stimulant response) was based on subjective patient medication histories rather than direct assessment.

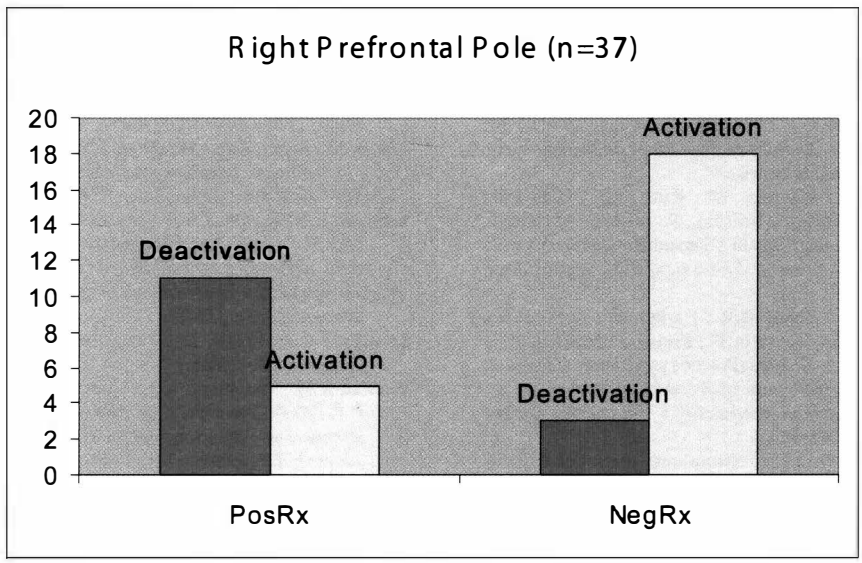
The patients in this study presented to an outpatient clinic that specializes in brain imaging. The nature of the clinic is such that it evaluates more complicated cases than a typical psychiatric outpatient clinic. Therefore, this sample is more likely to have had negative medication reactions, and such reactions may be more frequently documented than positive reactions. It is unlikely that these confounds skewed the analysis in the favor of the hypotheses.

FIGURE 3
Prefrontal Pole Activations and Deactivations Grouped by Stimulant Repsonse



Sensitivity: 0.71 **Measure of association: 10.78** ***p* = .001**

Specificity: 0.84



Sensitivity: 0.69 **Measure of association: 11.14** ***p* = .0008**

Specificity: 0.86

Another limitation is that our result is not generalizable to all concentration tasks. Although the Connors' CPT is a valid ADHD metric, other instruments are available that may induce different kinds of resource allocation.

Further, we recognize that our most interesting results derive from subsets of 36 and 37 of our 157 original patients as only these had significant pole deltas. However, this should not detract from the fact that the pole signatures we identified are highly correlated with stimulant response. Further analyses might make use of a more sensitive rating scale to identify a larger proportion of activations and deactivations.

Finally, we did not differentiate among CNS stimulants, in spite of their having somewhat differential effects on the brain (Challman & Lipsky 2000). However, we consider this fact as one of this study's strengths as it makes the results more generalizable.

In spite of the limitations inherent in its retrospective design, this study offers strong evidence of brain SPECT's utility in designing effective treatment regimens. It is important to note that that seventy-one out of the ninety-six patients in the negative response group met the DSM-IV ADHD criteria for inattention, and thirty-six of those also met the criteria for hyperactivity, meaning that considering behavioral symptoms alone was not enough to prescribe stimulants effectively. This suggests that brain imaging, when combined with behavioral symptoms, may have the potential to help guide treatment and improve response over and above current standards of practice, as common behavioral presentations do not necessarily have the same response profiles or underlying pathophysiology. Our hope is that these data will prompt prospective research looking at individuals meeting DSM-IV criteria for ADHD and directly measuring response to stimulant medications, further correlating outcomes with imaging.

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