Metabolic Patterns Associated with the Clinical Response to Galantamine Therapy: An FDG-PET Study in Alzheimer's Disease

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Abstract

Objectives: To differentiate the brain metabolic patterns associated with the spectrum of treatment responses to the cholinesterase inhibitor galantamine as visualized with [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET). **Background**: The regional metabolic correlates of treatment with cholinesterase inhibitors are unknown. **Methods**: This was a hypothesis driven, prospective, open-label, study of eighteen mild to moderate AD patients recruited from the community who were evaluated before, and after treatment with the cholinesterase inhibitor galantamine. Patients were given 16 to 24 mg of galantamine per day (based upon dosage tolerance) for 8 weeks. Major clinical evaluations included the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog), Mini Mental State Examination (MMSE), and Neuropsychiatric Inventory (NPI). Imaging was carried out using FDG-PET. The PET studies, registered to a probabilistic anatomic atlas were subjected to a voxel by voxel subtraction of the post-treatment minus pre-treatment studies within and across three patient subgroups: treatment responders, non-responders, and unchanged patients. Sub-Volume Thresholding (SVT) corrected random lobar noise to produce 3D functional significance maps. **Results**: The criterion for treatment response (≥ 4 point improvement from baseline in NPI total score) was met in 6 patients while the criterion for non-response (≥ 4 point worsening from baseline in NPI total score) was met in 5 patients; the 7 remaining patients fell between these criteria and were considered unchanged. The responders also had significantly improved ADAS-cog scores compared to the non-responder group ($p < 0.05$). The significant NPI subscale changes distinguishing the responders from the non-responders were agitation, euphoria, apathy, and irritability ($p \leq 0.05$) while ADAS-cog subscores showed significant improvement in learning and recognition between the two groups. The clinical benefits observed with galantamine were associated with metabolic activation of a lateral orbitofrontal defect at baseline in responders with an increase in thalamic activation that accompanied this and other brain changes. **Conclusion**: Future studies should explore the specificity of this distributed neural network across other cholinesterase inhibitor therapies.

Introduction

A major challenge presented to functional imaging studies seeking to map treatment effects on neuronal systems is distinguishing clinically relevant imaging patterns from statistically significant results unrelated to a patient's improvement, or decline. Computerized multi-voxel brain imaging analysis usually yields some statistically significant patterns that survive correction for multiple comparisons. Unless those patterns are shown to occur uniquely with a given clinical outcome little insight into the neural systems subserving that treatment outcome can be inferred. We,[1] and others,[2-6] have published studies on the resting functional imaging effects of cholinesterase inhibitors in the Alzheimer Disease (AD) brain in which patients with a spectrum of clinical responses are combined and, via group subtraction of post-treatment minus pre-treatment data, speculations are made about the neural systems affected by a drug. In such studies it is assumed that the average clinical response of the entire group will overwhelm the spectrum of responses. This assumption may be invalid.

Few functional studies have controlled for the spectrum of cholinesterase inhibitor response.[7, 8] The present study attempts to control for this spectrum of clinical response by evaluating pre- and post-treatment imaging data in subgroups of patients achieving *a priori* criteria for clinical response. Cognitive response may be less clinically relevant to a family suffering from AD than behavioral response.[9] Meaningful cognitive response, defined as a 7-point or greater improvement on the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-Cog)[10] rather than a 4 point improvement, occurs in at most a quarter of AD patients treated with tacrine, [11] donepezil,[12] galantamine,[13] or rivastigmine.[14] While significant behavioral improvement with treatment, defined as a four point or greater improvement in the Neuropsychiatric Inventory (NPI),[15] occurs in 41% of patients treated with cholinergic enhancement.[16] We defined clinical response as a four point or greater improvement in the NPI from baseline while non-responders were defined as worsening by four points or more; unchanged patients were defined as having a ±3 point change in the NPI with treatment which overlaps the range of change in placebo groups followed with the NPI in all double-blind clinical trials.

We evaluated the treatment related metabolic response to the cholinesterase inhibitor galantamine in AD using [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET).

Three hypotheses were tested in the current study. We have previously found that a pre-treatment lateral orbital frontal perfusion defect in AD patients with severe irritability, disinhibition, and euphoria may predict behavioral response to cholinergic therapy.[17] Thus, we sought to prospectively test this finding in a new patient group: Hypothesis 1) behavioral responders to galantamine treatment will have significantly hypo-metabolic lateral orbitofrontal regions compared to non-responders and unchanged patients at baseline that improves with treatment and will be associated with improved irritability, disinhibition, and euphoria. Galantamine is a relatively weak cholinesterase inhibitor but a potent nicotinic receptor modulator that lowers the resting membrane potential of cells possessing nicotinic receptors thereby facilitating firing.[18, 19] The highest concentration of nicotinic receptors in brain is in the thalamus[20] where the □4/ß2 receptors predominate on the thalamocortical glutaminergic afferents[21, 22] completing the final rely of the frontal-subcortical circuits. If galantamine transduces its clinical signal via nicotinic modulation then thalamic activation in responders might occur. Hypothesis 2) responders to galantamine will have significantly increased thalamic metabolism compared to non-responders and unchanged patients with treatment. The theory of a compensatory recruitment of increasing neural mass to accomplish a given task that becomes more challenging due to progressive dementia has emerged from functional activation studies in early stage patients compared to normal elderly.[23] Cholinergic agents may increase neural efficiency[24] in responders thereby decreasing the requirement to activate a greater mass of tissue to maintain the patient's behavioral repertoire. Hypothesis 3) responders to galantamine will have significantly decreased prefrontal metabolism post-treatment compared to pre-treatment.

Methods

Patients The study group consisted of 21 patients who presented for dementia evaluation to the University of California, Los Angeles (UCLA) Alzheimer's Disease Research Center or affiliated clinics and who met all study criteria (below), agreed to scanning with FDG-PET after signing an informed consent approved by the Human Subjects Protection Committee. All patients met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for

probable AD.[25] Inclusion criteria also included: a Mini Mental State Exam (MMSE)[26] score equal to 15 or above, a total NPI[15] score of at least 4, no history of psychiatric or non-AD neurological illness, being proficient in English to perform cognitive testing, age 50 or greater, a caregiver available to monitor and administer the medication and to accompany the subject to all clinical visits. All patients were stable on all concomitant medication for one month. Exclusion criteria included: all patients with a hematocrit <50%, a current or recent major psychiatric illness (i.e. manic depressive states, schizophrenia), treatment with clomipramine (Anafranil), significant, uncontrolled systemic illness (i.e. chronic renal failure, chronic liver disease, poorly controlled diabetes, or poorly controlled congestive heart failure), a history of alcoholism or substance abuse within the past year, use of other drugs that might interfere with the results of the study (i.e. benzodiazapines, barbiturates), and patients who were greater than 140% or less than 80% of their ideal body weight based on Metropolitan Life tables. Severity of the cognitive deficit was measured in all patients using the ADAS-Cog[10] and MMSE,[26] while behavioral deficits were measured with the NPI.[15]

Behavioral Assessment Caregivers were interviewed with the NPI following procedures previously described[15] in which screening questions for each behavior were first posed. The caregiver was asked if the behavior represented a change from that exhibited by the patient prior to the onset of the dementia and was present during the past month. If a positive response was obtained from the screening questions, then the behavioral domain was explored with scripted questions focusing on specific features of the behavioral disturbance. The caregiver then rated the behaviors; scores from 1-4 were obtained for the frequency and 1-3 for the severity of each behavior (a composite score for each domain was the product of the frequency and severity subscores; maximum = 12). The NPI has been shown to be both valid and reliable;[15] raters received specific training in NPI administration and were retrained periodically to prevent drift. The ten domains assessed by the NPI are: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and abnormal motor behavior. The criterion for behavioral response was defined as an improvement of ≥4 points in the total post-treatment NPI score from baseline.[16]

Statistical Clinical Analysis. A histogram of NPI data reveals that composite scores do not generate a normal distribution. Multiplying the frequency (1-4) by the severity (1-3) subscores will not produce a composite score of 5, 7, 10 or 11. The non-normal distribution of NPI data, and the low number of subjects producing MMSE and ADAS-cog data, supports the use of a bootstrap analysis[27] to evaluate significance. Bootstrap analysis combines raw scores, for any given behavior or score, of an entire dataset and randomly samples a number of these scores equal to the number making up the groups comprising the dataset. A mean difference score is then calculated from the randomly comprised samples. This procedure is then repeated 1000 times on the dataset, producing a distribution of possible scores. The *observed* mean differences are then compared to this distribution of the *possible* mean difference scores between groups, for each NPI item or clinical score. The probability of finding the observed mean difference based upon the mean difference generated by resampling is recorded. This process was repeated 10 times for each score to arrive at an average probability value resulting from 10,000 resampling combinations for each comparison. If the observed difference is greater than 95% of the differences expected from random resampling in the bootstrap method, the observed difference was judged to be statistically significant at the 0.05 value.

Scanning Procedure Scanning of patients with FDG-PET occurred at baseline (week 0) and after completion of 8 weeks of galantamine therapy. The patient's family signed an informed consent for scanning and the patient assented to the procedure. While in the scanner in a dimmed room, the patient received a 5 mCi intravenous injection of [F-18] fluorodeoxyglucose (half-life = 110 min.) according to a protocol previously described.[28] Imaging commenced 40 minutes after administration of FDG and lasted for 60 minutes, with > 2 million counts per plane. Image resolution after reconstruction had a maximum of 3.6 mm full width at half maximum (FWHM) in plane at center and 4.5 mm at 20 cm off center. A calculated attenuation correction was used.[29] Details of the FDG-PET method have been previously described.[30-32]

Image Processing. Spatial alignment of all 36 PET datasets was accomplished via 12 parameter affine registration.[33] To minimize spatial deformation of the PET data all studies were first aligned to one randomly selected target to obtain an "average PET" which in turn was aligned,

via 12 parameter affine registration, to the AD probabilistic atlas.[34] To minimize resampling of data, the two above registration fields were concatenated and applied to each PET dataset. The relative FDG-PET scans of each patient then underwent linear intensity normalization, on a voxel by voxel basis, to the global mean intensity value of the pre- and post-treatment groups' thalamic values. This global normalization step did not alter the intersubject data variance or the mean inter-group differences.

Once all normalized datasets were in the common atlas space, a voxel by voxel subtraction was conducted between the pre- and post-treatment groups. When across group comparisons were accomplished an equal number of datasets must be in each group; in these cases the group with the lowest number was matched to the other group of an equal number of the same sex and similar aged patients. Sub-Volume Thresholding (SVT) was used to create statistical maps of these subtraction results as previously described.[35] Briefly, after the first SVT step identifies globally significant regions within the probabilistically partitioned atlas, the second step maps the location of voxels, with a difference Z-score above 2.5, in those regions. This is a standard procedure in most functional statistical mapping techniques with two exception: 1) voxel location tests are run *only* over those regions identified by the global search in step one; and 2) variance estimates are pooled over subjects and across voxels. A Bonferroni correction was employed on the voxel-wise comparisons as previously described[17] when no regional hypothesis was tested.

Results

Eighteen of the initial 21 patients were able to tolerate the initial 8mg daily dosage of galantamine and move on to the 16 or 24 mg per day dose for four weeks yielding a total of 8 weeks of therapy. The baseline demographic and clinical characteristic for the treatment responders, non-responders, and unchanged groups are shown in Tables 1 and 2, no significant differences were found for these baseline profiles. One patient in each group was only able to tolerate 16mg – 20mg per day of galantamine after the initial 8mg per day starting dose; all other patients were able to tolerate 24mg per day. The criterion of a ≥4 point improvement on the NPI total score was found in 6 patients while

5 patients were found to be non-responders (≥4 point decline) with 7 patients remaining unchanged (±3 change) during the 8 weeks of treatment. Figure 1 shows the changes in the clinical assessments observed during the course of galantamine treatment. Non-responders showed significant worsening in both cognition and behavior compared to the responder group with agitation, euphoria, apathy, and irritability being the key behaviors to significantly worsen ($p < 0.05$) while attention, learning, and recognition were the cognitive domains to significantly worsen ($p < 0.05$); of note praxis improved for the non-responders during treatment.

Tables 1 and 2 and Figure 1

Figure 2 reveals the Bonferroni corrected statistical maps for the hypometabolic regions found in responders and non-responders compared to unchanged patients at baseline. AD atlas Talairach[36] compatible locations of the most significant voxels in these comparisons are shown. Areas of note with significant decreases in metabolism compared to unchanged patients in the responder group are the right lateral orbitofrontal cortex (z= -5) which improves with treatment as predicted in hypothesis 1; note that this finding is not present in the non-responder group. Hypometabolism at baseline in the responders, compared to the unchanged group that resolved with treatment, was also found in the right anterior cingulate (x = +4) that was not present in the non-responder group. Bilateral caudate head hypometabolism occurred with treatment in the responders compared to the unchanged group (z = +7, y = +4), and was present in the non-responders at baseline and after treatment. In relation to hypothesis 2 the non-responders possessed bilateral anterior medial thalamic hypometabolism compared to the unchanged group at baseline (z = +7) that worsened with treatment.

Figure 2

Figure 3 reveals the Bonferroni corrected statistical maps for both increased and decreased metabolism in the responders compared to non-responders at baseline and after treatment. At baseline

responders had greater metabolism than non-responders in the sub-thalamic region on the left extending into the midbrain and dorsal pons (y = -19.5) as well as the medial precuneus on the right (y = -41.5); the precuneus finding persisted with treatment. Significant decreases in metabolism at baseline in the responders compared to the non-responders were found in the right lateral orbitofrontal region as predicted by hypothesis 1 (y = +39.5) along with bilateral posterior orbitofrontal hypometabolism (y = +4.5); these relative defects did not resolve with treatment as predicted, however a left anteriomedial orbitofrontal increase did occur with treatment (y = +44.5) that had not been previously hypo-metabolic in comparison. Another area of decreased metabolism at baseline in the responders compared to the non-responders was the cingulate on the right greater than the left (y = -9.5, -19.5, and -27.5); similar to the lateral orbitofrontal region these differences persisted with treatment. However, more anterior bilateral cingulate regions did increase with treatment compared to the non-responders (y = +16.5 through –8.5) that were not hypo-metabolic at baseline. Hypometabolism with treatment in responders compared to non-responders arose in the left amygdalar areas (y = -4.5 and –8.5) as well as in the superior cerebellum bilaterally (y = -54.5).

Figure 3

Figure 4 reveals uncorrected statistical maps for the within group comparisons of the responders and non-responders after treatment compared to baseline; these maps should only be considered with reference to the three *a priori* hypotheses. Hypothesis 3 finds support in this comparison where significant hypometabolism occurred in responders, but not in non-responders, after treatment in the anterior medial orbitofrontal region (y = +17.5); however, increased metabolism uniquely occurred in the responders in the left lateral orbitofrontal, and left medial thalamus supporting hypotheses 1 and 2.

Figure 4

Discussion

This is the first study to evaluate treatment related resting metabolism in AD across the spectrum of clinical response. Two past studies have used functional imaging to evaluate cholinesterase inhibitor treatment in responders. Potkin, et al[7] found prefrontal and hippocampal metabolic increases from baseline in rivastigmine responders compared to decreases in non-responders and placebo-treated patients over a 26 week study. However, qualitative, not objective measures of treatment response were used. An additional study by Venneri, et al[8] using ^{99m}Tc-HMPAO single photon emission computed tomography (SPECT) at baseline, 3 months, and six months after rivastigmine treatment defined clinical response as beneficial behavioral changes from baseline reported by caregivers, global clinical impression, stable or improved NPI scores, or improvement of at least two points on the MMSE score. After 6 months of rivastigmine treatment the responder group improved on their NPI total score by 1.8 points, and on the MMSE by 2.4 points. Statistical maps of responder's baseline perfusion compared to the 6 month post-treatment scans revealed a peak increase in the anterior cingulate bilaterally and left dorsolateral parietofrontal regions. Non-responders lost 2.1 points on the MMSE and worsened by 3.9 points on the NPI while demonstrating diffuse right greater than left perfusion declines across the entire brain. No evaluations were done comparing responders to nonresponders in that study.

The present study prospectively tested three hypotheses. The first hypothesis was fulfilled in that responders had a significant hypometabolic defect in the (right) lateral orbitofrontal region at baseline that resolved with treatment compared to unchanged patients (Figure 2, z = -5) and increased after treatment compared to non-responders (Figure 3, y = +39.5) while being associated with a significant improvement in agitation, euphoria, apathy, and irritability compared to non-responders. These orbitofrontal findings even survived Bonferroni correction. However, the within group responder's subtraction seen in Figure 4 shows a left, not right, lateral orbitofrontal increase in metabolism with treatment (z = +2), with the bilateral medial regions becoming hypometabolic with treatment. This complex finding suggests a functional disassociation between the medial and

lateral orbitofrontal cortex. Indeed, the medial and lateral divisions of the orbitofrontal cortex have distinctly different efferent and afferent connectivity, the lateral being involved with attaching emotional valence to the external environment while the medial division participates in coordinating the organisms internal milieu and when stimulated produces a visceral response.[37] Perhaps the opposite metabolic states of these two divisions of the orbitofrontal cortex subserve different aspects of the behavioral improvement noted on the NPI.

The second hypothesis was also supported by this study. In Figure 4 at z = +2 we find an increase in the anterior medial thalamus on the left with treatment compared to baseline in the responders which is not seen in non-responders who had this same region hypometabolic both at baseline and after treatment compared to unchanged patients (Figure 2, z = +7, and x = -5). Even in the responder versus non-responder condition the left anterior thalamus is increased with treatment in responders and survived a Bonferroni correction. This robust finding supports a role for the activation of the limbic thalamus in patients responding to galantamine treatment and suggests a modulatory role for galantamine on the nicotinic receptors which have their highest concentration in the thalamus[20] where the α4/ß2 receptors predominate on the thalamocortical glutaminergic afferents[21, 22] that complete the final rely of the frontal-subcortical circuits. Future studies should explore the orbitofrontal subcortical network in similar treatment designs with principal component analysis to see if that distributed network it linked to a specific behavioral profile, or if other cholinesterase inhibitors have similar effects.

The third hypothesis was also supported by this study. However, the only robust support comes from the uncorrected maps on Figure 4 at y = +17.5. Given that stimulation of this medial orbitofrontal cortex produces visceral signs and symptoms it is unclear from these present data if the explanation that motivated this hypothesis—that a decrease in the neural mass necessary to perform a given function is accomplished by an activating drug— should be accepted or rejected.

In summary, this is the first study to evaluate treatment related resting metabolism in AD across the spectrum of clinical response. Although a lateral orbitofrontal defect at baseline in responders appears to reverse with galantamine treatment and an increase in thalamic activation

accompanies this and other brain changes, more refined statistical mapping methods are needed to dissect the distributed neural networks associated with the spectrum of clinical effects of cholinesterase inhibitor therapy.

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Table 1. Baseline demographic and cognitive characteristics of the three patient groups, no significant difference was found in any domain.

	Responders	**Unchanged**	**Non-Responders**
	mean(sd)	mean(sd)	mean(sd)
Gender	2males/4females	3males/4females	3males/2female
Age	77.4(4.7)	74.4(10.5)	77.4(5.8)
MMSE	25.2(3.0)	22.7(3.5)	23.0(3.0)
ADLs	65.2(11.3)	68.9(5.3)	71.2(3.7)
ADAS-cog Total	25.7(13.6)	25.7(5.5)	26.2(13.4)
Learning	6.7(1.4)	6.4(1.4)	7.0(2.1)
Naming	0.5(0.5)	0.3(0.5)	0.4(0.8)
Recall	6.8(2.1)	8.9(1.2)	7.6(2.9)
Commands	0.5(0.5)	0.3(0.5)	0.8(0.7)
Drawing	0.8(0.6)	1.0(0.8)	0.8(0.4)
Praxis	0.7(1.4)	0.1(0.3)	0.8(0.7)
Orientation	1.3(1.7)	2.1(1.8)	2.2(1.5)
Recognition	5.8(3.3)	5.1(1.0)	3.6(2.4)
Language	0.5(1.0)	0.4(0.5)	1.0(1.5)
Comprehension	0.3(0.7)	0.1(0.3)	0.4(0.8)
Fluency	0.7(1.0)	0.6(0.7)	0.8(1.6)
Instruction Recall	0.8(1.7)	0.3(0.5)	0.8(1.6)
Attention	17.7(5.2)	15.6(5.4)	16.0(3.6)

MMSE = Mini Mental State Exam, ADLs = Activities of Daily Living, ADAS-cog = Alzheimer's Disease Assessment Scale cognitive portion.

Table 2. Baseline behavioral characteristics of the three patient groups, no significant difference was found in any domain.

	Responders	**Unchanged**	**Non-Responders**
	mean(sd)	mean (sd)	mean (sd)
NPI Total	14.8(6.5)	9.7 (6.1)	6.4 (5.2)
Delusions	1.3(2.8)	0.4 (0.7)	0.0 (0.0)
Hallucinations	0.2(0.3)	0.1 (0.3)	0.0 (0.0)
Agitation	1.0(1.1)	1.7 (2.1)	1.6 (1.5)
Depression	2.7(3.5)	0.6 (1.0)	1.4 (1.4)
Anxiety	3.7(3.7)	1.4 (2.0)	0.8 (1.2)
Euphoria	0.7(1.4)	0.6 (1.4)	0.8 (1.6)
Apathy	3.7(4.1)	1.6 (1.4)	0.8 (1.2)
Disinhibition	0.0(0.0)	0.6 (1.4)	0.2 (0.4)
Irritability	2.0(2.7)	1.6 (2.1)	1.2 (1.5)
Abnormal Motor	1.7(1.6)	1.4 (2.3)	0.2 (0.4)

NPI = Neuropsychiatric Inventory.

Figure Legends

Figure 1. The mean change scores during galantamine therapy are shown on top for the main clinical outcomes. The mean change scores during galantamine therapy are shown in the middle for the composite (frequency x severity) NPI sub-scores. The mean change scores during galantamine therapy are shown on the bottom for the ADAS-cog subscores.

_____

a = $p < 0.001$ across all three clinical groups.

b = $p \leq 0.05$ in non-responders compared to responders.

c = $p \leq 0.05$ in non-responders compared to both unchanged and responders, and their own baseline.

d = $p \leq 0.05$ in non-responders compared to their own baseline.

e = $p \leq 0.05$ in non-responders compared to responders and their own baseline.

f = $p \leq 0.05$ in non-responders compared to unchanged group.

g = $p \leq 0.05$ in non-responders compared to responders and in responders compared to their own baseline.

Figure 1

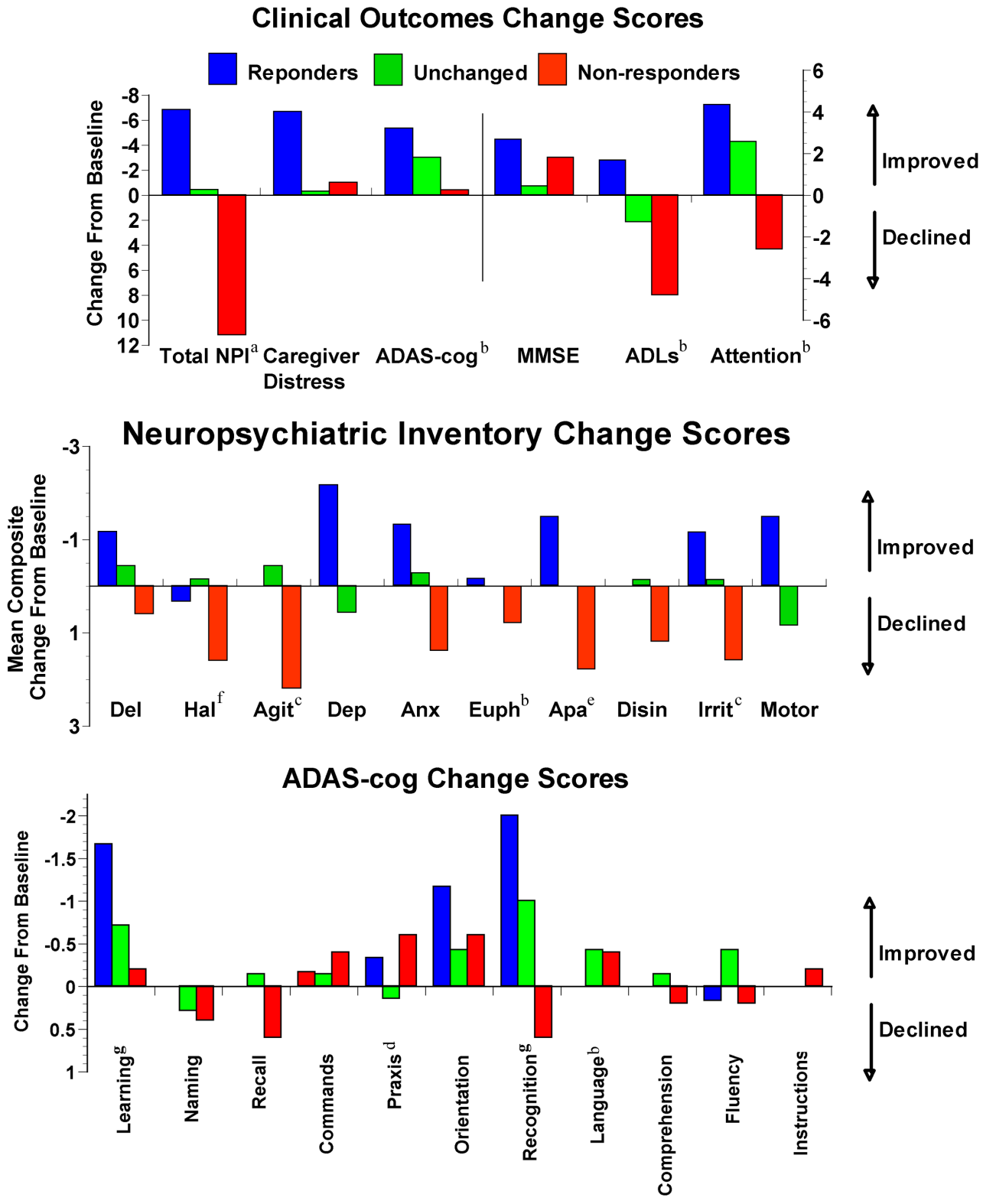

Clinical Outcomes Change Scores
Reponders
Unchanged
Non-responders
Change From Baseline
-8
-6
-4
-2
0
2
4
6
8
10
12
6
4
2
0
-2
-4
-6
Improved
Declined
Total NPI[a]
Caregiver Distress
ADAS-cog[b]
MMSE
ADLs[b]
Attention[b]
Neuropsychiatric Inventory Change Scores
Mean Composite Change From Baseline
-3
-1
1
3
Improved
Declined
Del
Hal[f]
Agit[c]
Dep
Anx
Euph[b]
Apa[e]
Disin
Irrit[c]
Motor
ADAS-cog Change Scores
Change From Baseline
-2
-1.5
-1
-0.5
0
0.5
1
Improved
Declined
Learning[g]
Naming
Recall
Commands
Praxis[d]
Orientation
Recognition[g]
Language[b]
Comprehension
Fluency
Instructions

Figure 2.

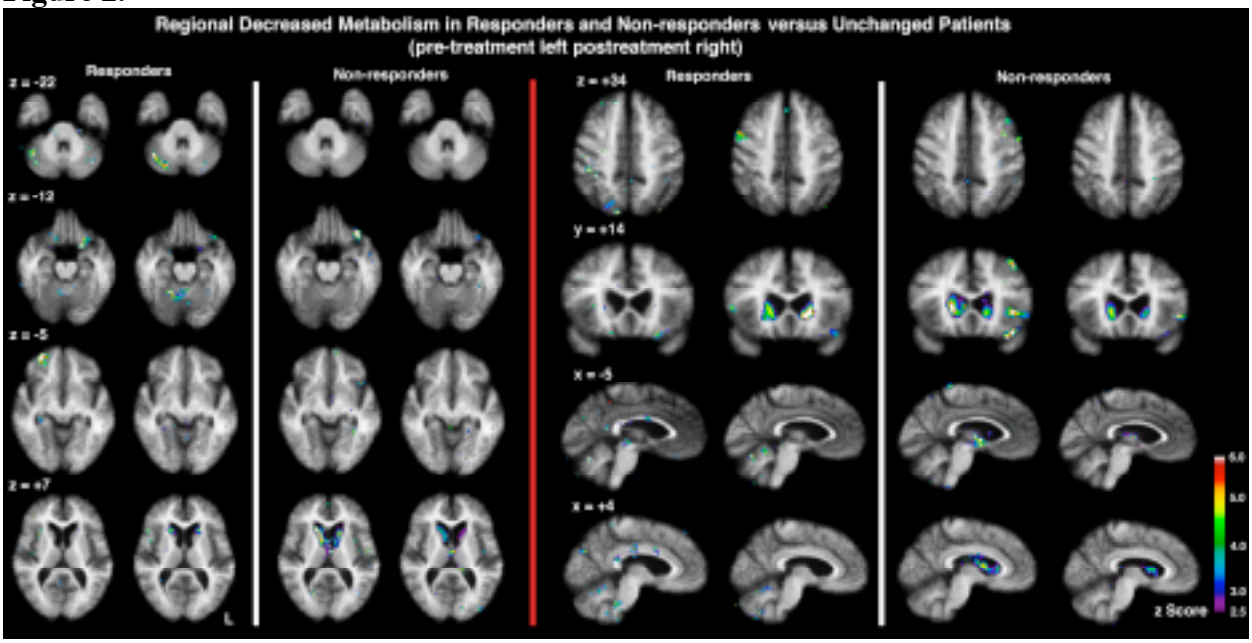

Regional Decreased Metabolism in Responders and Non-responders versus Unchanged Patients
(pre-treatment left posttreatment right)
Responders
Non-responders
z = -22
z = -12
z = -5
z = +7
z = +34
Responders
Non-responders
y = +14
x = -5
x = +6
z Score

Figure 3.

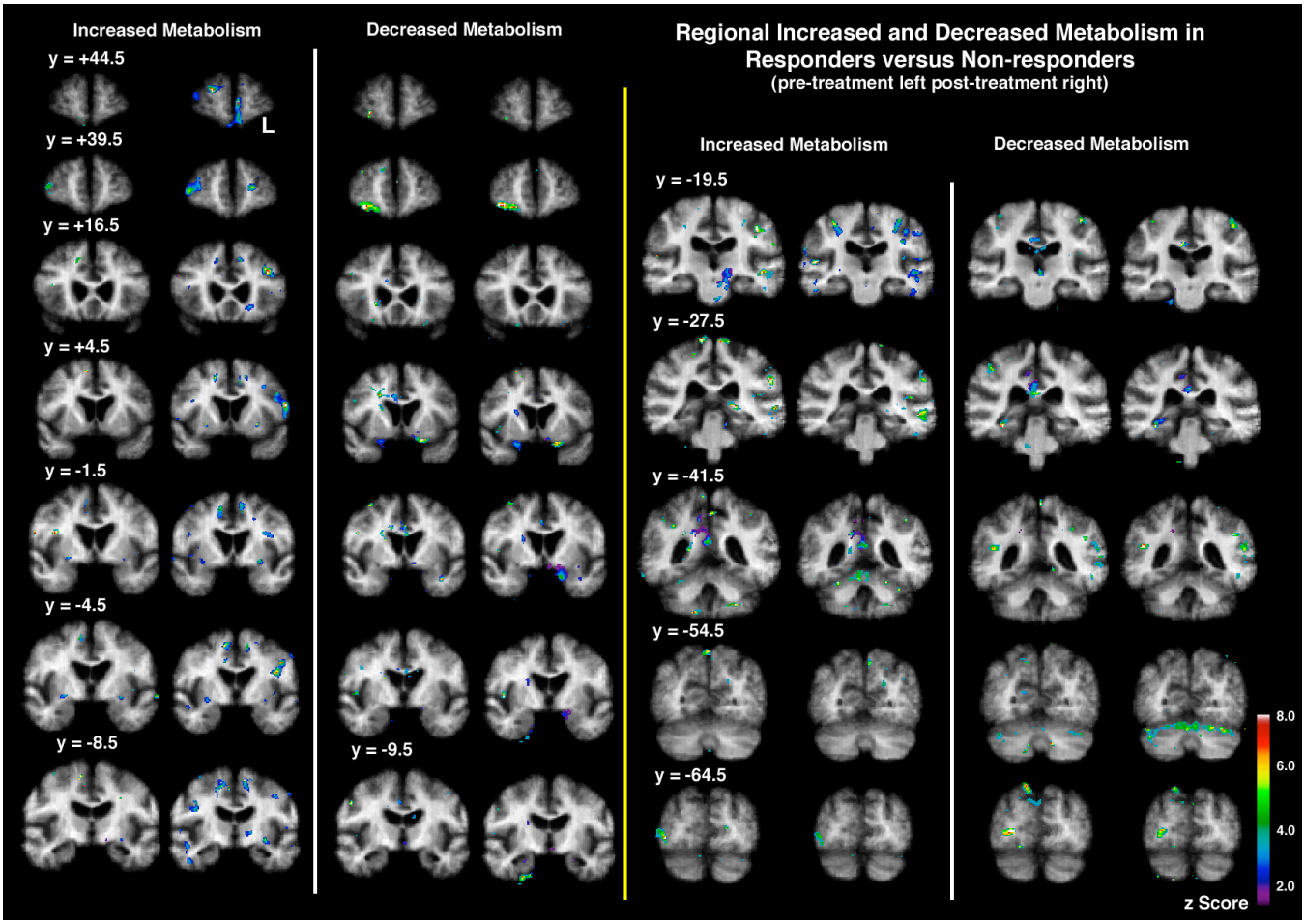
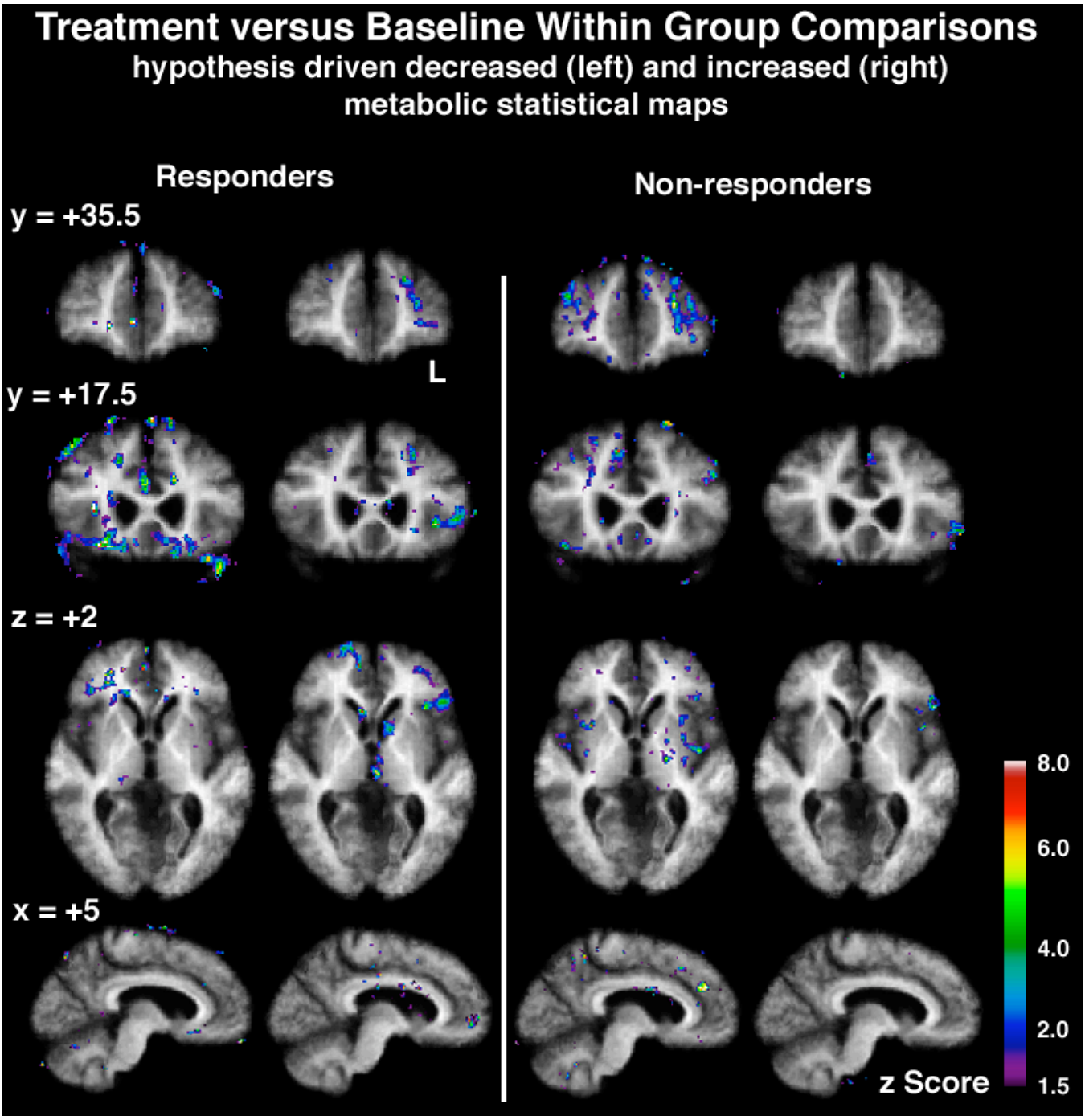

Increased Metabolism
Decreased Metabolism
Regional Increased and Decreased Metabolism in Responders versus Non-responders
(pre-treatment left post-treatment right)
Increased Metabolism
Decreased Metabolism
y = +44.5
y = +39.5
y = +16.5
y = +4.5
y = -1.5
y = -4.5
y = -8.5
y = -9.5
y = -19.5
y = -27.5
y = -41.5
y = -54.5
y = -64.5
L
8.0
6.0
4.0
2.0
z Score

Figure 4.


Treatment versus Baseline Within Group Comparisons
hypothesis driven decreased (left) and increased (right)
metabolic statistical maps
Responders
Non-responders
y = +35.5
y = +17.5
z = +2
x = +5
L
8.0
6.0
4.0
2.0
1.5
z Score