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FDG-PET in Semantic Dementia after 6 Months of Memantine: an Open-Label Pilot Study

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Abstract

Objectives—To follow up on the increases we reported in normalized metabolic activity in salience network hubs from a 2-month open label study of memantine in frontotemporal dementia (FTD).

Methods—We repeated fluoro-deoxyglucose positron emission tomography (PET) after 6 months of drug use and subjected the data to an SPM analysis to reveal clusters of significant change from baseline. We also sought correlations between changes in behavioral disturbances on the Frontal Behavioral Inventory (FBI).

Results—Recruitment of one progressive nonfluent aphasia and one behavioral variant FTD precluded statistical analysis for any FTD subtype other than semantic dementia. The baseline-to-6-month interval showed increased normalized metabolic activity in the left orbitofrontal cortex ($p < 0.002$) for 5 participants with semantic dementia. The 2–6 month interval revealed a late increase in normalized metabolic activity in the left insula ($p < 0.013$), right insula ($p < 0.009$), and left anterior cingulate ($p < 0.005$). The right anterior cingulate showed both an initial increase and a delayed, further increase (2–6 month, $p < 0.016$). FBI scores worsened by 43.3%. One participant with semantic dementia opted not to continue memantine beyond 2 months yet showed similar FDG-PET increases.

Conclusions—Increases in normalized cortical metabolic activity in salience network hubs were sustained in SD over a 6-month period. Since one participant without medication also showed

these changes, further investigation is recommended through a double-blind, placebo-controlled study with FDG-PET as an outcome measure.

Keywords

frontotemporal dementia; metabolism; PET scan; semantic dementia

Introduction

Frontotemporal degeneration (FTD) represents a spectrum of debilitating neurodegenerative disorders characterized by an early age at onset, rapidly declining course, significant behavioral disturbance and aphasia. To date, FTD is treated symptomatically by a variety of general psychotropic medications including antidepressants, anxiolytics and antipsychotics that aim to alleviate symptoms such as anxiety and aggression (Kaye, et al.). However, no pharmacological intervention has been approved by Health Canada or the Food and Drug Administration to specifically target FTD or alter the disease course.

Prior studies have reported the use of fluoro-deoxyglucose positron emission tomography (FDG-PET) as a sensitive method to detect hypometabolic activity in cortical regions connected with FTD (Salmon, et al. ; Salmon, et al. ; Starkstein, et al. 1994). These regions include orbitofrontal, dorsolateral prefrontal, anterior cingulate, insula and anterior temporal cortex. Researchers have even elucidated a correlation between the prototypic aberrations of behavioral variant FTD and specific hypometabolic prefrontal regions functionally linked together as the “salience network” (Zhou, et al.). In our previous study, we demonstrated significantly increased normalized metabolic activity in hubs of the salience network in sixteen FTD patients after completing 7–8 weeks of open-label memantine treatment. When stratified by FTD subgroup, increases were seen in the right insula and left OFC in semantic dementia (SD) (n=8) and in the left thalamus and left anterior cingulate in behavioral variant frontotemporal dementia (bvFTD) (n=7). However, there were no significant changes on behavioral and functional rating scales observed over the short treatment period (Chow, et al. 2011).

Most dementias progress slowly over years, yet significant variability can be observed in behaviour and cognition from month-to-month. Positive pivotal trials of anti-dementia therapy have typically been 6 months in duration. In accordance, the pivotal trial for memantine in moderate to severe Alzheimer’s disease (AD) patients demonstrated reduced clinical deterioration over a 6 month period (Reisberg, et al. 2003).

The purpose of this study was to continue measuring metabolic activity in the participants who extended memantine use from the end of the 2-month study to 6 months. We sought sustained changes in normalized metabolic activity, particularly in salience network hubs, or whether additional changes occurred after the first 2 months. We hypothesized that participants would sustain the increase in normalized metabolic activity from baseline in salience network hubs at 6 months of memantine therapy, either at the same level as their 2-month results or greater. We also checked for beneficial behavioral outcome at 6 months, and if any behavioral benefits correlated with changes in specific volumes of interest (VOI).

Methods

Subjects

Seven participants with FTD from our previous study opted to continue open-label treatment with memantine 10 mg administered twice a day until a third FDG-PET assessment at 6 months (see Figure 1). The participants had originally been recruited by Baycrest, Toronto

Western and Sunnybrook clinics after obtaining ethics board approval at Baycrest and the Center for Addiction and Mental Health. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. Informed consent was obtained and participants had been screened for eligibility based on inclusion and exclusion criteria that ascertained diagnosis and safety for the procedures (Chow et al, 2011). Eligible participants were willing to return for the PET scan 6 months after starting memantine. Figure 1 shows the recruitment flow chart. Eight of the 17 participants who completed the 7 week study continued until the 6-month follow-up, with 7 on memantine and 1 off memantine. The memantine group consisted of 5 participants with SD, 1 with bvFTD, and 1 with progressive nonfluent aphasia (PNFA), determined by established diagnostic criteria (Neary, et al.). Another participant (005) continuing without memantine had a diagnosis of SD, bringing the total to 6 participants with SD.

Drug administration

Participants receiving memantine continued at a dose of 10 mg orally twice a day consistently for months 2–6, after titration over the first month. Follow-up for adverse effects was undertaken at the time of the third PET scan and through spontaneous report by participants and informants. All but one participant with SD opted to complete a 6-month course of open-label treatment with memantine hydrochloride. FDG-PET scans were performed at baseline, 7 weeks, and 6 months. Those who continued memantine received the last dose the morning of the 3rd PET scan.

A Drug Safety and Monitoring Board was appointed by Baycrest and reviewed the study semi-annually. No serious adverse events took place between the 2 month and 6 month PET scans. However, one participant who did not continue due to increased agitation took a full 8-week course before stopping (see Figure 1). Another participant's caregiver withdrew consent to participate close to the end of the study due to escalation of a behavioral problem.

Neuroimaging and analysis

Participants underwent high resolution FDG-PET scanning 40 minutes after administration of a 5mCi intravenous bolus of FDG. FDG-PET data were coregistered to the previously acquired baseline MRI scan. A single T1-weighted template was created to represent the average of the coregistered MRIs from the 7 participants who completed a 6-month course of memantine. To maintain consistency with our first study on the 2-month effects of memantine on this patient group, we again used SPM2 to seek significant increases and decreases in clusters of at least 10 voxels below an uncorrected P value of 0.05. Because the t-test requires a minimum of 6 participants, our most consistent sample for the analysis consisted of the 6 participants with semantic dementia, which included participant 005, who had not continued memantine beyond month 2 and might therefore skew the analysis away from significant findings. A separate analysis was run featuring one participant with PNFA and the 5 with SD who had taken memantine for the 6-month study period to corroborate the VOIs yielded by the first t-test. Normalized FDG signal intensity values in VOI were determined for the one participant with bvFTD for reporting, but the sample available did not allow for formal between-groups analysis for SD versus PNFA or SD versus bvFTD.

Secondary outcome measures and analysis

Participants were evaluated by their informants on several clinical rating scales at baseline, 8 weeks and 6 months. These included the Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Dementia Rating Scale (CDR), Frontal Behavioral Inventory (FBI), Sum of Boxes CDR-FTD, Stereotyping Rating Inventory (SRI), and the Frontal Assessment Battery (FAB). Due to small sample size and the potential for non-normal distribution of the

data, we compared baseline and 6-month scores (following the SPM analysis of FDG-PET data) using Wilcoxon Signed Ranks tests for $N = 6$ SD participants and also for all 8 participants.

Results

Increased normalized metabolic activity in the OFC was sustained over the entire baseline to 6 month interval for the 6 participants with SD, regardless of memantine use (See Table 1, Figure 2A). The previously reported increase in right insular activity between baseline and 2 months was not observed for SD between baseline and 6 months for SD.

The 2–6 month interval revealed a relatively late increase in normalized metabolic activity in the right insula ($p < 0.005$), left insula ($p < 0.013$) (Figure 2B), and left anterior cingulate ($p < 0.005$) (Figure 2C). The right anterior cingulate VOI showed both an initial increase and a delayed (2–6 month, $p < 0.0016$) increase within all SD, including 005, who had not continued memantine (Figure 2D, Figure 3). Signal intensities in the left insula for participants 016 with PNFA and 018 with bvFTD are shown in Figure 3 for comparison.

The 2-tailed Wilcoxon Signed Rank tests comparing behavioral and functional rating scale scores revealed a significant worsening on the FBI (43.3%) between baseline and 6 months for the 6 SD patients but no significant changes for the mixed sample ($N = 8$).

Discussion

This study has shown a sustained yet modest increase in normalized metabolic activity in salient network hubs for participants with SD. Of the salient network hubs, the right anterior cingulate may have been the most responsive, increasing significantly over 2 time intervals; arguably the cluster size for the left anterior cingulate may also reflect high response, yet we are limited by the absence of a placebo group. Whereas the right insula increased normalized metabolic activity had figured predominantly in a mixed FTD sample from the previous study, we only demonstrated a delayed increase in right insular activity for 6 participants with SD and this may have occurred independently of memantine use.

The VOIs with increased normalized metabolic activity in SD participants corresponded with those found in our 2-month study in the same FTD subgroup, surviving the reduction in sample size from the original 8 to 5 who continued the protocol extension to a third PET scan. It may be surprising to readers that the insular areas and not anterior temporal poles showed the significant changes in our SD group, and this may be attributable to the small sample size, but the extended results in the insular VOIs may serve as some replication of the 2-month findings. Uptake was measured for the entire brain, but SPM did not show any significant increases in the anterior temporal VOIs. In functional imaging studies, partial volume effects must be considered. It is possible that we had no findings in the anterior temporal VOIs because the atrophy intrinsic to semantic dementia has lowered the detectable signal beyond a range where change can be significant. Otherwise, we have shown in prior work that the imaging data collected with our high resolution research tomograph does not lead to different results when subjected to partial volume corrections. (Chow, et al. 2009)

Also consistent with the 2-month trial, there were no improvements on measures of behavior or cognition after 6 months. If anything, the worsened score on the FBI implies that increased normalized metabolic activity in selected salient network hubs was not strategically placed relative to brain regions most affected in SD and therefore does not address behavioral decline in SD. Alternatively, it could be argued that the modest improvement in normalized metabolic activity, although significant, may not have been

large enough to improve clinical performance. The absence of measurable clinical benefits is consistent with other previously discussed clinical trials of memantine in FTD (Diehl-Schmid, et al. 2008; Vercelletto, et al. 2010).

The late increase in activity in the left insula, right insula, and left anterior cingulate between 2 and 6 months suggests that memantine may have long-term effects in normalizing cortical metabolic activity in salience network hubs in SD. The similarity of increased normalized metabolic activity seen in participant 005 without memantine implies that the effects of memantine may last beyond the treatment course. Certainly, the sample size leaves the results insufficient to generalize to the semantic dementia population, whether assessing for long-term use of the medication or post-medication effects. One could argue for a larger SD study population to submit to the study protocol.

As above, one of the principal limitations in this study was the sample size. In addition to the reduced SD sample, we recruited only 1 PNFA and 1 bvFTD, which prevented comparisons among FTD subtypes. The fact that the baseline to 2-month increase in right insular normalized metabolic activity was not sustained over the entire study period may have been driven by the attrition in SD participants from $N = 8$ to 6 in the second study interval. In inputting such a small sample into SPM, we accepted the risk that even one outlier could bias the comparison. Figure 3, exemplifying the signal intensities of the participants, implies but does not guarantee that there was no outlier effect. Despite our sample consisting mainly of SD, we did not test participants using aphasia test scores beyond the semantic fluency item on the FAB, and so the effect of memantine on language has not been examined.

As in our previous report, the lack of a placebo-treated control group precluded definitive conclusions on whether memantine's metabolic activation effects provide any benefit in SD. Although we found sustained increases in normalized metabolic activity, they ranged between 4% and 19%. By comparison, Potkin et al. showed a 32.5% increase in hippocampal metabolism in AD responding to rivastigmine after 26 weeks of therapy (Potkin, et al.). Further, it is debatable whether our small percentage increases in normalized metabolic activity bear any clinical significance in the context of actual worsening on the FBI.

To date, no other studies have investigated the effects of memantine therapy over a 6-month period using FDG-PET in FTD. The methodology has been applied more frequently in studies of AD. One such study reported increased metabolic activity in temporal and inferior parietal cortex on FDG-PET after 10 weeks of memantine (Sultzer, et al.). Another study used FDG-PET to show increased cerebral metabolic response to citalopram after two months of galantamine treatment (Smith, et al. 2009). Alzheimer's disease responders to rivastigmine showed increased activity on FDG-PET, along with decreased deterioration in cognitive measures, when compared against non-responders and participants taking placebo (Potkin et al.). The results of these trials are encouraging for the use of FDG-PET as an outcome measure for anti-dementia pharmacotherapy, but if larger placebo-controlled clinical trials do not show clinically measurable benefits, it will remain to investigate whether the improvement in FDG-PET corresponds with better survival or slower decline over time.

Conclusion

Extension of observation for memantine benefits beyond 2 months showed increases in salient network hubs on FDG-PET but without clinical correlations in a small group of participants with SD. It remains to be tested whether memantine's effects on salience

network metabolic activity would result in a clinically correlated improvement or stabilization in other forms of FTD. Based on the insula and anterior cingulate VOIs identified in this study, double-blind, placebo-controlled study in bvFTD might be the most likely study design to yield a result.

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Key points

- Fluoro-deoxyglucose PET imaging measures changes in the cortical metabolic activity of regional contributors to the salience network that are hit hardest in frontotemporal dementia.
- FDG-PET activity in salience network hubs increased in participants with semantic dementia after 6 months of memantine use.
- Frontal Behavioral Inventory scores worsened over the same time period.

Figure 1.
Recruitment Flowchart

Figure 2.

Volumes of interest where the t-contrast showed increased normalized metabolic activity ($p < 0.05$) for clusters of at least 10 voxels. A shows the left OFC, which increased between baseline and 6 months. B–C show VOIs with significant increases appreciated between 2 and 6 months. B denotes the left insula with red crosshairs and right insula with white crosshairs. Vertical color bars show t statistic values. Images are shown on a T1-weighted template representing the composite average of the 7 participants who took memantine for 6 months.

Figure 3. Changes in FDG normalized metabolic signal intensity for the left insula at 0, 2 and 6 months (N=8). Five participants with SD showed an increase, although 005 (dashed line) opted to discontinue medication after month 2. The PNFA case (016) showed a decrease despite using memantine, and the participant with bvFTD (018) a slight increase.

Table 1

Volumes of interest showing increased normalized metabolic activity for semantic dementia, in decreasing order of cluster size (n=6). False Discovery Rate (FDR)-corrected p values were performed for small volume adjustment.

Volume of interest	Peak voxel coordinates			Cluster Size	Un-corrected voxel p value	FDR-corrected p value	Mean change in normalized metabolic activity	Paired t-statistic	95% CI, p value
	x	y	z						
SD (n=6)									
Baseline vs. 6 months									
Left OFC	-24	58	-14	52	0.001	0.902	+6.51%	6.23	3.67-8.74, 0.001
Right anterior cingulate	10	46	10	48	0.004	0.902	+7.01%	6.51	4.52-10.42, 0.001
2 vs. 6 months									
Right anterior cingulate	20	46	32	211	0.016	0.861	+15.8%	4.54	6.63-23.92, 0.006
Right Insula	40	8	14	221	0.005	0.874	+4.88%	2.58	-0.023-10.19, 0.049
Left Insula	-36	6	10	110	0.013	0.874	+6.87%	2.30	-0.88-15.91, 0.07
Left anterior cingulate	-10	44	38	847	0.005	0.874	+7.57%	3.61	2.17-12.86, 0.015