Alzheimer's & Dementia: Translational Research & Clinical Interventions 5 (2019) 254-263

Alzheimer's & Dementia

Featured Article

Effects of pioglitazone on mnemonic hippocampal function: A blood oxygen level–dependent functional magnetic resonance imaging study in elderly adults

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Abstract

Introduction: Mitochondrial dysfunction is implicated in the pathophysiology of Alzheimer's disease (AD). Accordingly, drugs that positively influence mitochondrial function are being evaluated in delay-of-onset clinical trials with at-risk individuals. Such ongoing clinical research can be advanced by developing a better understanding of how these drugs affect intermediate brain phenotypes associated with both AD risk and pathophysiology.

Methods: Using a randomized, parallel-group, placebo-controlled design in 55 healthy elderly volunteers, we explored the effects of oral, low-dose pioglitazone, a thiazolidinedione with promitochondrial effects, on hippocampal activity measured with functional magnetic resonance imaging during the encoding of novel face–name pairs.

Results: Compared with placebo, 0.6 mg of pioglitazone (but not 2.1 mg, 3.9 mg, or 6.0 mg) administered daily for 14 days was associated with significant increases in right hippocampal activation during encoding of novel face–name pairs at day 7 and day 14, relative to baseline.

Discussion: Our exploratory analyses suggest that low-dose pioglitazone has measurable effects on mnemonic brain function associated with AD risk and pathophysiology.

Keywords: Alzheimer's disease; Blood oxygen level–dependent functional magnetic resonance imaging; Mnemonic hippocampal activity; Pioglitazone; Thiazolidinediones

NCT no.: 01456117.

A.R.K. has nothing to disclose. J.R.B., K.A.W-B., and B.L.P. received salary support from Takeda Pharmaceutical Company Limited through a research agreement between the company and Duke University. D.K.B. is an employee of Zinfandel Pharmaceuticals, Inc. S.K.B. and M.K. were employees of Takeda Development Center Americas, Inc., when this work was done. A.R.H. has received a consultant payment from Zinfandel Pharmaceuticals, Inc. in 2010. He also received supplemental salary support from Takeda Pharmaceutical Company Limited through a research agreement between the company and Duke University.

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https://doi.org/10.1016/j.trci.2019.05.004

1. Background

There is widespread recognition that Alzheimer's disease (AD) is a looming global public health crisis, and new interventions are urgently needed [1,2]. Despite significant attention, no novel therapy with a new chemical entity for AD has been approved since 2003. Recent research [3] has demonstrated that changes in brain architecture and chemistry precede the appearance of the memory deficits that are the hallmark of AD. These findings have stimulated interest in therapeutic strategies targeting these premorbid processes in the hope of delaying the onset of clinical symptoms.

Thiazolidinediones (TZDs) are agonists of the peroxisome proliferator-activated receptor gamma (PPARγ) and are approved for the treatment of adult-onset diabetes mellitus (AODM). PPARγ is highly expressed in neurons throughout the mammalian brain [4], and TZDs have been shown to affect biological pathways that may play a role in AD [5]. In particular, PPARγ stimulation with low doses of TZDs has been shown to promote mitochondrial biogenesis in neuronal-derived cells *in vitro*, where it protects these cells from glucose deprivation-induced cell loss [6]. Furthermore, epidemiologic studies report that use of either of the TZDs pioglitazone or rosiglitazone is associated with a reduction in the incidence of dementia in subjects with AODM [7]. Thus, TZDs represent a novel therapeutic candidate in delay-of-onset trials for individuals at near-term risk of developing AD.

As it is often unclear whether a molecular target has been engaged, seeking evidence of action in associated functions of the brain, in the appropriate time frame with the correct stimulus/dose, is important to address before the initiation of clinical trials. Accordingly, we used a randomized, parallel-group, placebo-controlled design in healthy elderly volunteers to explore possible effects of immediate-release (IR) pioglitazone on a core risk-related brain phenotype, namely episodic memory-related hippocampal activity, measured with blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI). We specifically explored hippocampal effects of IR pioglitazone at 7 and 14 days after treatment initiation compared with baseline at 0.6 mg, 2.1 mg, 3.9 mg, and 6.0 mg. Our focus on memory-related hippocampal activity reflects four interrelated considerations. First, hippocampal dysfunction is related to the etiology and pathophysiology of AD [8]. Second, hippocampal dysfunction is associated with genetic variants conferring susceptibility to AD [9]. Third, hippocampal activity is highly dependent on energy metabolism supported by mitochondrial function [10]. Finally, PPARγ is highly expressed in the hippocampus [11].

2. Methods

2.1. Overview

This was a randomized, parallel-group, placebo-controlled pharmacologic BOLD fMRI study targeting episodic memory-related hippocampal activation. Each participant underwent a baseline scan (day 1) and then received as an oral solution their first dose of either pioglitazone (at one of four doses) or placebo. Daily treatment with either drug or placebo was continued for 14 days. Additional scans were completed at 7 and 14 days post baseline. A single-blind protocol was employed for the 3.9 mg dose, which was completed before the other arms of the study to verify the efficacy of the protocol at a mid-range dose before conducting the full-scale exploration of the dose range. Up to 12 participants in this part were to receive the 3.9 mg dose. No placebo was planned. After completing the 3.9 mg dose arm, the placebo and 0.6 mg, 2.1 mg, and 6.0 mg dose arms were subsequently completed using a double-blind protocol, in which 48 participants were to be randomized into equally sized placebo and dose groups. The study was conducted in compliance with the institutional review board, Good Clinical Practice regulations, and ethical standards of the Declaration of Helsinki.

2.2. Participant recruitment and screening

Participants were recruited primarily from the Alzheimer's Disease Prevention Registry of Joseph and Kathleen Bryan Alzheimer's Disease Research Center at Duke University, a research-ready cohort of approximately 3500 cognitively healthy adults from the local community who are interested in being involved in studies of brain health [12]. Recruitment was augmented by referrals from Duke University physicians and through the use of multiple modes of advertisement conducted by X Factor, a research participant recruitment firm. Eligibility criteria comprised (1) men and women aged 55–83 years, inclusive; (2) normal cognition; and (3) adequate vision to see stimuli for the fMRI task. Normal cognition was defined as the absence of a memory complaint and scores $\geq$25 on the Montreal Cognitive Assessment following educational adjustment [13], delayed recall score of $\geq$4 on the 10-item Consortium to Establish a Registry for Alzheimer's Disease Word List task Memory (CERAD-WLM) [14,15], and a score of $\leq$180 seconds on the Trail Making Test Part B [16,17].

Ineligibility criteria comprised (1) diabetes and taking insulin or a PPARγ agonist or HbA1c >6%; (2) routinely taking proton-pump inhibitors, H2 receptor antagonists, antacids, or other selected medications; (3) contraindication for MRI; (4) taking an investigational drug within the prior 6 months; (5) history of macular edema, degeneration, or any maculopathy; and (6) history of selected medical conditions such as cancer that required chemotherapy within the prior 2 years, significant congestive heart failure, significant psychiatric illness or treatment for these illnesses including depression, and conditions that can cause dementia, such as stroke.

2.3. Drug compounding and pharmacokinetics

Pioglitazone HCl 0.3 mg/mL oral solution and the placebo for pioglitazone solution were compounded at the study

site. Assessments of drug stability in the dosing solution were conducted as appropriate. The administration of the study drug in an aqueous citric acid solution (10 g anhydrous citric acid per 500 mL water) provided adequate masking of the taste of the drug substance, which maintained the study blind.

One blood sample (6 mL) for the measurement of pioglitazone plasma concentration was collected after dosing for each participant immediately after collection of the clinical laboratory test blood sample on day 14/final visit. The assessment of pioglitazone plasma concentrations in all participants confirmed drug compliance and appropriate assignment of the regimen (i.e., active or placebo). Plasma concentrations of pioglitazone were measured through a validated high-performance liquid chromatography with tandem mass spectrometry detection method (PPD, Middleton, WI, USA) with a plasma concentration range of 1 to 1000 ng/mL.

2.4. fMRI task

Our fMRI task (Fig. 1) consisted of encoding and subsequent recall of novel face–name pairs [18]. A distractor task (odd/even number identification) was interleaved between encoding and recall blocks to prevent information from being maintained in working memory. During each of four encoding blocks, participants viewed six novel face–name pairs for 3.5 seconds each. During each of the four recall blocks, participants viewed six faces, each presented for 2 seconds and immediately followed an incomplete name stem for 1 second, during which they were required by forced-choice to determine if the name was correct or incorrect. A 1-second intertrial interval was used during recall blocks. During each of the four distractor blocks, participants viewed six different numbers for 3.5 seconds each and were required to determine if the numbers were odd or even. Three versions of the paradigm with nonoverlapping face–name pairs were utilized for each participant in a pseudorandomized order. Participant performance (i.e., accuracy and reaction time during distractor and recall blocks) was recorded using an MRI-compatible button box.

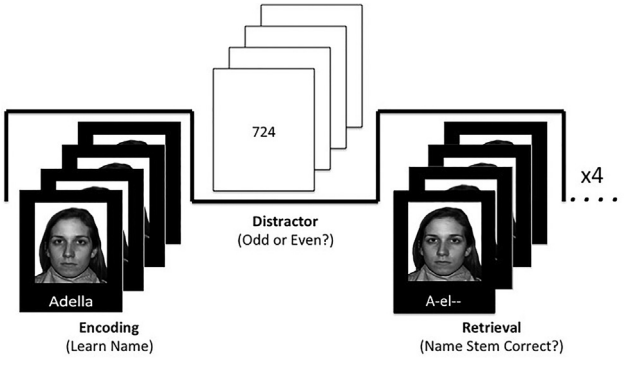

Fig. 1. Exemplar stimuli and block structure of the episodic memory fMRI paradigm. See section 2.4 for details. Abbreviation: fMRI, functional magnetic resonance imaging.

2.5. BOLD fMRI data acquisition

Each participant was scanned using a research-dedicated GE MR750 3T scanner equipped with high-power high-duty-cycle 50 mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil was used for parallel imaging at a high bandwidth up to 1 MHz at the Duke-UNC Brain Imaging and Analysis Center. A semiautomated high-order shimming program was used to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure–posterior commissure plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifact (repetition time/echo time/flip angle = 2000 ms/30 ms/60°; field of view = 240 mm; 3.75 × 3.75 × 4.00 mm voxels; interslice skip = 0). Four initial radiofrequency excitations were performed (and discarded) to achieve steady-state equilibrium. To allow for spatial registration of each participant's data to a standard coordinate system, structural images were acquired in 34 axial slices coplanar with the functional scans (repetition time/echo time/flip angle = 7.7 s/3.0 ms/12°; voxel size = 0.9 × 0.9 × 4.0 mm; field of view = 240 mm, interslice skip = 0).

2.6. BOLD fMRI data preprocessing

SPM8 (www.fil.ion.ucl.ac.uk/spm) was used for preprocessing. Images for each participant were realigned to the first volume in the time series to correct for head motion, spatially normalized into a standard stereotactic space (Montreal Neurological Institute [MNI] template) using a 12-parameter affine model (final resolution of functional images = 2 mm isotropic voxels) and smoothed to minimize noise and residual difference in gyral anatomy with a Gaussian filter, set at 6 mm full-width at half-maximum. Voxel-wise signal intensities were ratio-normalized to the whole-brain global mean.

Variability in single-participant whole-brain functional volumes was determined using the Artifact Recognition Toolbox (http://www.nitrc.org/projects/artifact_detect). Individual whole-brain BOLD fMRI volumes meeting at least one of the two criteria were assigned a lower weight in determination of task-specific effects: (1) significant mean volume signal intensity variation (i.e., within-volume mean signal ± 4 standard deviations of mean signal of all volumes in the time series) and (2) individual volumes in which scan-to-scan movement exceeded 2 mm translation or 2° rotation in any direction.

After preprocessing, linear contrasts employing canonical hemodynamic response functions were applied for each individual to the contrast of *Encoding blocks* > *Distractor blocks*, which elicits the greatest memory-related hippocampal activation [18,19].

2.7. Test–retest reliability

The test–retest reliability of our fMRI task was evaluated by calculating the intraclass correlation coefficient (ICC) for hippocampal clusters exhibiting significant task-related activation across baseline and day 7 in the placebo group (n = 11). Specifically, the ICC was determined for extracted mean BOLD percent signal change (PSC) values from hippocampal activation clusters using ICC (3,1), which was estimated using a linear mixed-effect model for repeated measures (participants vs. time) with a consistency criterion defined as follows:

$$\frac{MS_S - MS_E}{MS_S + (k-1)MS_E}$$

in which MS_S and MS_E are the participant's mean square and error mean square from the linear mixed-effect model, respectively, and k is the number of time points (here, $k = 2$).

2.8. Effects of dose analyses

Here, we describe analyses conducted to determine the effects of pioglitazone dose on hippocampal activation. Ancillary analyses detailed in the Clinical Study Report are not included. Individual contrast images derived from the preprocessed data were entered into a 5 (placebo and 0.6 mg, 2.1 mg, 3.9 mg, 6.0 mg doses) × 3 (baseline, Day 7, Day 14) repeated-measures analysis of variance (ANOVA), controlling for age and sex, to identify drug-by-time interaction effects on encoding-related activity in left and right hippocampal regions of interest (ROIs). Bilateral hippocampal ROIs were selected from the predefined Automated Anatomical Labeling masks available in the Wake Forest University Pickatlas Tool, version 1.04 [20]. A combined statistical height threshold of $P < .05$ and spatial extent threshold of 59 contiguous voxels for left hippocampus and 56 contiguous voxels for right hippocampus was applied to all analyses to control for type I error at a cluster-level threshold of $P < .05$. The spatial extent thresholds were determined for each ROI via 10,000 Monte Carlo simulations conducted using the ClusterSim program in Analysis of Functional NeuroImages with the mixed-model autocorrelation function parameters set to the within-ROI residual estimates of [0.88, 4.38, 1.45] for the left hippocampus and [0.98, 3.98, 0.33] for the right hippocampus (http://afni.nimh.nih.gov/afni). Any significant drug-by-time interaction effects were deconstructed using pairwise post hoc t-tests applied to extract mean BOLD PSC values from hippocampal activation clusters identified in the repeated-measures ANOVA.

2.9. Partial volume correction

To avoid partial volume effects, where differences in the volume of a target structure can confound estimates of BOLD activation [21], we estimated the volumes of the right and left hippocampus for all participants and scans using the FreeSurfer longitudinal stream [22]. The mean volume estimates for each participant and scan were entered as covariates of no interest in all analyses of hippocampal BOLD activation.

3. Results

3.1. Participants

A total of 564 individuals were contacted to complete the telephone screening interview after they were sent a study introductory letter or responded to a study advertisement. Of these, 61 met eligibility requirements and were enrolled in the study. Complete data were available for 55 participants; four had incomplete data due to inability to tolerate the MRI or do the fMRI task, and, as described below, two had incomplete data due to a treatment-emergent adverse event (TEAE). Another six individuals met eligibility criteria, but the study quota had already been met so they did not participate. A total of 130 refused participation and 367 were ineligible. The most frequent reasons for ineligibility were psychiatric medications or illnesses (n = 146), taking proton-pump inhibitors or H2 receptor antagonists or other excluded medications (n = 88), and MRI contraindications (n = 24). Within the 55 participants included in the final analyses, there were no significant differences between the five groups (i.e., placebo, 0.6 mg, 2.1 mg, 3.9 mg, 6.0 mg) in any study-relevant demographic or cognitive function measures (See Supplementary Table 1 in the Supplementary Material).

3.2. Drug tolerance and subjective reports

As noted previously, 2 of 61 participants (4.1%) experienced a TEAE during the study: one participant in the pioglitazone 0.6 mg group experienced a TEAE of foreign body (root canal drill bit broke off in tooth), and one participant in the pioglitazone 2.1 mg group experienced a TEAE of pneumonia. Both of these TEAEs were considered mild in intensity and unrelated to study drug by the investigators. No other TEAEs leading to study drug or study visit discontinuation, or other significant adverse events, were reported in this study. No participant had a clinical laboratory test result, vital sign measurement, 12-lead electrocardiography result, or physical examination finding after dosing that was considered clinically significant or that was reported as a TEAE by the investigators.

3.3. Pharmacokinetics

At day 14/final visit, 12 of 12 participants who had received placebo had no detectable levels of pioglitazone in plasma, and 47 of 47 participants who received pioglitazone and were included in the analyses had detectable levels of pioglitazone in plasma. These results confirmed the treatment assignments of the study participants. Pioglitazone

plasma concentrations were generally highest for participants who received pioglitazone 6.0 mg and lowest for participants who received pioglitazone 0.6 mg, as anticipated.

3.4. Task performance

There were no significant differences in task performance among the five groups at baseline ($F = 1.607$, $P = .187$), and no significant group-by-time interaction effects on accuracy ($F = 1.235$, $P = .287$) or reaction time ($F = .743$, $P = .653$). There was a significant main effect of time on accuracy ($F = 6.32$, $P = .004$), which likely reflects increasing familiarity with the task demands over successive scans.

3.5. BOLD fMRI task effects

As generally observed in fMRI studies of episodic memory encoding [19] and consistent with previous work using the specific fMRI task in our study [18], the contrast of *Encoding blocks > Distractor blocks* revealed robust bilateral hippocampal activation (Fig. 2) averaged across all participants and scans: left hippocampus ($P < .0001$; cluster size = 565 voxels; MNI coordinates for max voxel: x = −24, y = −32, z = −4) and right hippocampus ($P < .0001$; cluster size = 583 voxels; MNI coordinates for max voxel: x = 24, y = −28, z = −8).

3.6. Test–retest reliability

Test–retest analyses were conducted on extracted mean BOLD PSC values from the max voxels of significant activation clusters across the baseline and day 7 scans in the placebo group: left hippocampus ($P < .0001$; cluster size = 416 voxels; MNI coordinates for max voxel: x = −26, y = −36, z = 2) and right hippocampus ($P < .0001$; cluster size = 232 voxels; MNI coordinates for max voxel: x = 22, y = −32, z = −2). These analyses revealed good reliability of our task in eliciting mnemonic hippocampal activation (right hippocampus ICC = .61, left hippocampus ICC = .67; Fig. 3).

3.7. Correlations between hippocampal activity and task performance

Regression analyses were conducted across all groups and scans to examine the general relationship between the magnitude of activity within hippocampal ROIs during encoding blocks and subsequent accuracy during recall blocks as well as reaction times for correctly recalled face–name pairs. Overall, reaction times for correctly recalled face–name pairs were significantly negatively correlated with activity in both the left and right hippocampus during encoding (see Supplementary Fig. 2 in the Supplemental Material). A positive correlation between recall accuracy and activity in the left hippocampus during encoding was also observed but did not reach cluster-level significance (see Supplementary Fig. 3 in the Supplemental Material).

3.8. Drug effects on hippocampal activity

A 5 × 3 repeated-measures ANOVA revealed a significant group-by-time interaction effect (Fig. 4) on encoding-related activity in the right hippocampus ($F = 3.25$, $P = .003$; cluster size = 59 voxels; MNI coordinates for max voxel: x = 34, y = −32, z = −10). Pairwise post hoc t-tests conducted on the extracted mean BOLD PSC values from the right hippocampal cluster (Fig. 5) revealed significantly increased right hippocampal activation in the 0.6 mg dose group from baseline to day 7 as well as from baseline to day 14. In contrast, a significant decrease in right hippocampal activation from day 7 to day 14 was observed in the placebo group ($T = -2.4$, $P = .037$). No other pairwise comparisons produced significant differences in hippocampal activation.

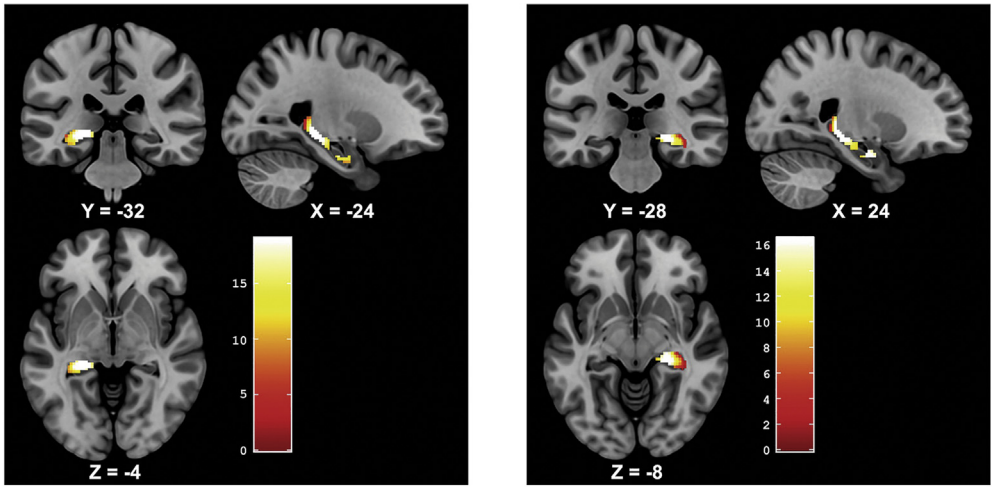

Fig. 2. Encoding-related activation clusters in the left and right hippocampus across all participants and scans ($P < .05$, corrected for family-wise error across hippocampal ROIs). Color bar represents t-scores. See section 3.5 for cluster- and voxel-level statistics. Abbreviation: ROI, region of interest.

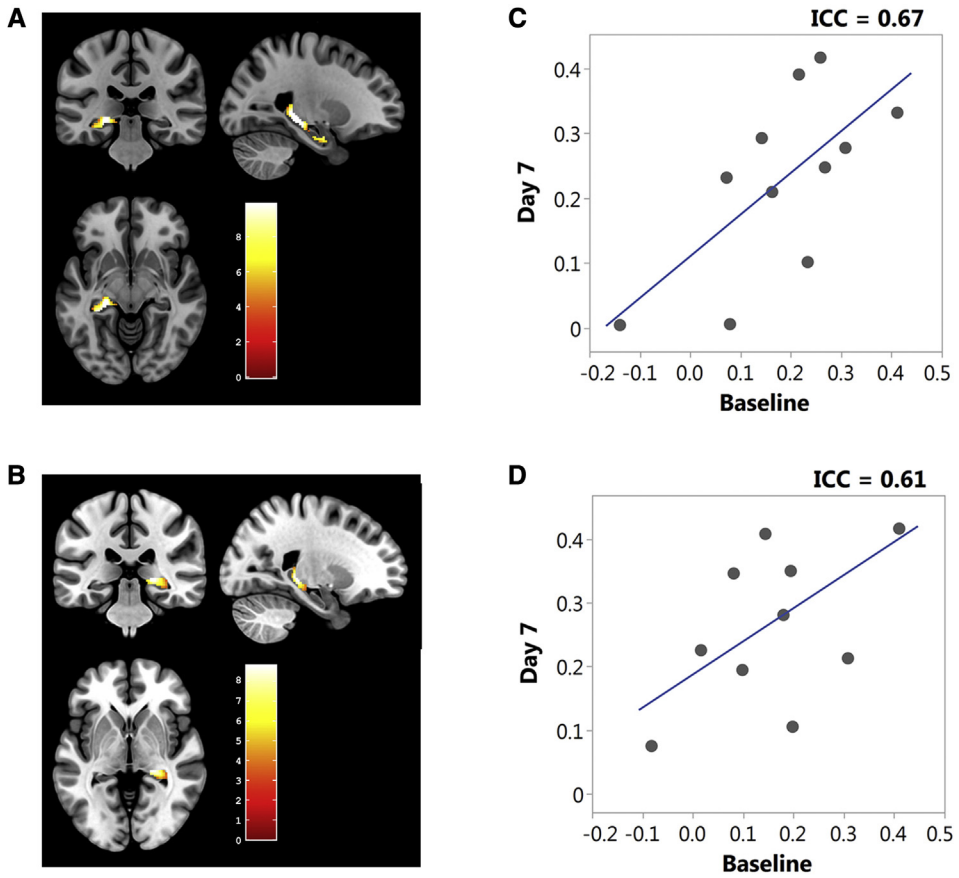

Fig. 3. Test–retest reliability of our fMRI task for eliciting episodic memory-related hippocampal activation. Average activation across baseline and day 7 scans in the placebo group for the left (A) and right (B) hippocampus. ICC for the mean extracted BOLD PSC values from the maximum voxels in the activation clusters in the left (C) and right (D) hippocampus. Color bars represent t-scores. See section 3.6 for cluster- and voxel-level statistics. Abbreviations: BOLD, blood oxygen level–dependent; fMRI, functional magnetic resonance imaging; ICC, intraclass correlation coefficient; PSC, percent signal change.

Exploratory whole-brain analyses revealed no significant effects of any dose relative to placebo over time on memory-encoding activity using corrected thresholds (family-wise error, $P < .05$) that account for multiple comparisons across all voxels. However, whole-brain analyses at a less stringent threshold (voxel-wise $P < .05$, uncorrected; and 10 contiguous voxels) revealed a pattern of increasingly distributed (i.e., nonspecific to the hippocampus) activity over time at higher doses in comparison with placebo (see Supplementary Fig. 4 in the Supplemental Material).

4. Discussion

Our analyses indicate that treatment with relatively low doses of pioglitazone is associated with alterations in episodic memory-related hippocampal activity in healthy elderly adults. Specifically, there were significant increases relative to placebo in right hippocampal activation during encoding of novel face–name pairs in the 0.6 mg dose group from baseline to day 7 as well as from baseline to day 14. Exploratory whole-brain analyses suggested that, in comparison with placebo, higher doses of pioglitazone were associated with nonspecific increases in distributed activity during encoding. Thus, the lowest tested dose of pioglitazone was associated with not only the lone significant increase in hippocampal activity but also the most circumscribed (i.e., targeted) effect on this core circuitry supporting memory encoding.

Consistent with prior findings in health elderly participants [23,24], the magnitude of activity in a left hippocampal cluster during encoding was positively correlated with better memory (i.e., accuracy during recall blocks), although this association did not survive correction for multiple comparisons. This is not unexpected given the background of generally high accuracy across participants and scans and thus limited interindividual variability. However, where there was considerably more variability in performance across participants and scans, the magnitude of activity in clusters within both left and right hippocampus predicted significantly faster recall of correct face–name pairs. Thus, the increased hippocampal activity during encoding associated with the lowest dose of pioglitazone is generally consistent with promnemonic effects, albeit in the absence of significant group differences in task

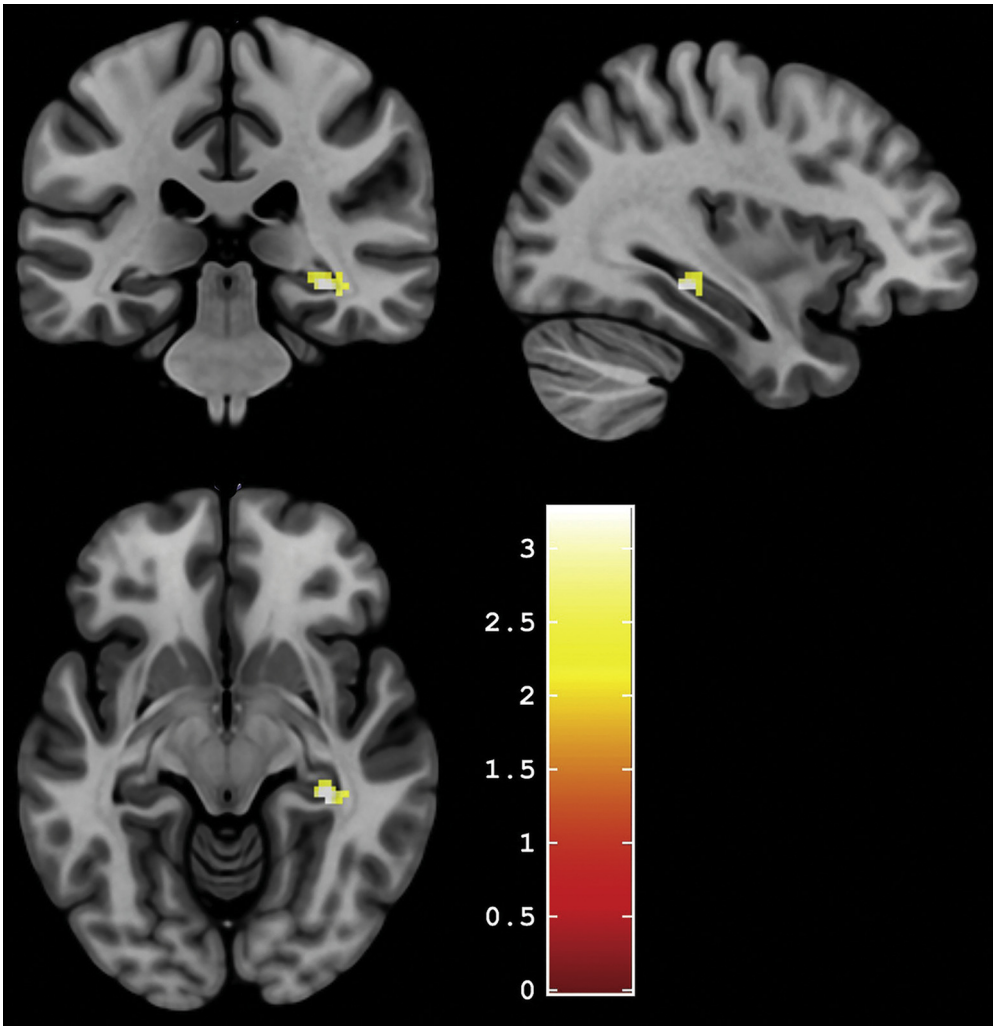

Fig. 4. Encoding-related activation cluster in the right hippocampus exhibiting a significant group-by-time interaction effect ($P < .05$, corrected). Color bar represents t-scores. See section 3.8 for cluster- and voxel-level statistics.

performance. Observing significant group differences in brain function in the absence of observable differences in behavior is not uncommon in fMRI studies and, in fact, can be considered a relative strength of this approach in detecting target effects during exploratory stages of drug development.

The effect of 0.6 mg pioglitazone on increased mnemonic hippocampal activity is consistent with the broader function of TZDs as agonists of PPARγ, the stimulation of which promotes mitochondrial biogenesis [25]. This effect is further consistent with the ability of low-dose TZDs to protect against glucose deprivation-induced neuronal loss [6]. It is possible that such promitochondrial and bioenergetic effects of TZDs underlie the increased hippocampal activity we observed at 0.6 mg. The absence of such effects at relatively higher doses may reflect increasing nonspecific effects of pioglitazone on neuronal metabolism beyond that necessary to support episodic encoding through the hippocampus. The more distributed, nonspecific pattern of activity observed in our exploratory whole-brain analyses is consistent with this speculation, but more work is needed to understand any nonlinear effects. Nevertheless, the observed effects of 0.6 mg pioglitazone on mnemonic hippocampal activity could represent one biological mechanism through which TZDs may contribute to reduced incidence of dementia in AODM [7].

Our observed effects of low-dose pioglitazone on mnemonic hippocampal activity should be considered in the context of the following limitations, which could be addressed in future research. First, it is unclear to what extent our observed drug effects in healthy elderly volunteers will generalize to at-risk individuals or those with early signs of disease. Studies with such populations would help address not only this limitation but also to what extent the observed effects are dependent on a minimum level of intrinsic mnemonic hippocampal activity (i.e., are there floor effects?). It is further possible that drug-associated effects on hippocampal function in at-risk individuals or those early in the disease time course may manifest as relatively decreased

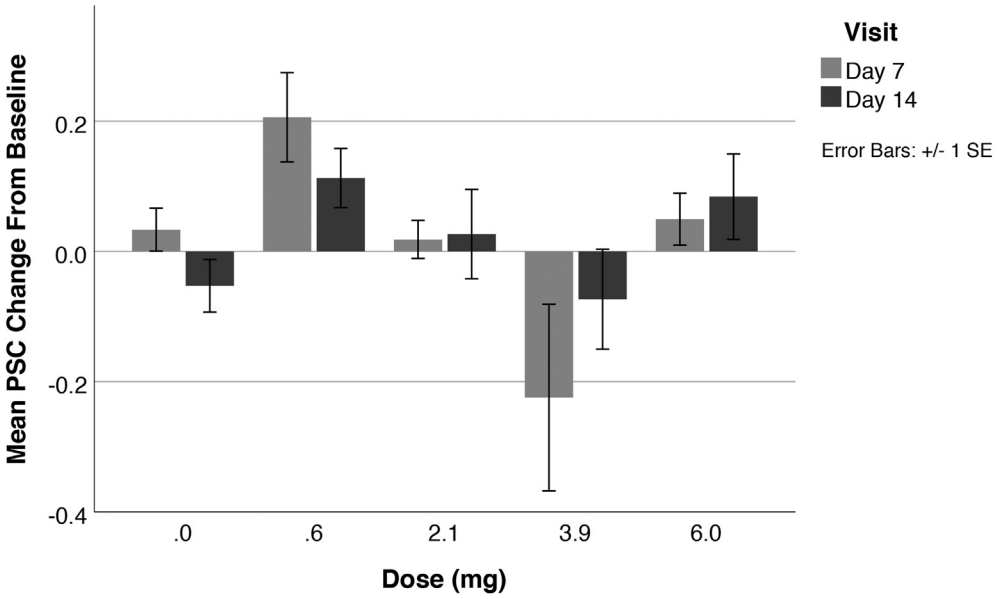

Fig. 5. Extracted mean BOLD PSC values from baseline as a function of group from the right hippocampal cluster identified in the repeated-measures ANOVA. Pairwise post hoc t-tests revealed significant differences between baseline and both day 7 ($t = 3$, $P = .013$) and day 14 ($t = 2.49$, $P = .032$) activation in the 0.6-mg group only. Abbreviations: ANOVA, analysis of variance; BOLD, blood oxygen level–dependent; PSC, percent signal change; SE, standard error.

activation (i.e., more efficient processing [26]) as well as improved memory performance, which was absent in our healthy elderly volunteers. Second, additional pharmacologic fMRI and, ideally, molecular studies are needed to better understand the nonlinear effects of low-dose pioglitazone on hippocampal activity. It is possible that, in keeping with other psychotropic agents (e.g., dopamimetics), the effects of pioglitazone and possibly other TZDs on behaviorally relevant brain function conform to an inverted U-shaped curve, wherein an optimal range is associated with beneficial effects [27]. Individual differences in baseline function of the molecular signaling pathways targeted by pioglitazone, such as may be associated with common genetic variants [28], could further shape the optimal range of therapeutic responses.

These limitations notwithstanding, our observation that low-dose pioglitazone can have measurable effects on brain function associated with AD risk and pathophysiology provides support for the general strategy of using TZDs in efforts to delay the onset of AD in at-risk individuals. Although these brain effects were not manifested at the level of task performance in our sample of healthy elderly adults, corresponding promnemonic behavioral effects may be observed in otherwise healthy elderly individuals with prolonged drug administration. The observed potentiation of neural function may also support maintenance and, possibly, improvement of memory in at-risk individuals, including those possessing genetic variants conferring susceptibility for AD. In fact, the pharmacologic fMRI data summarized herein were used, in part, to inform dose selection for a phase 3 global, clinical study to assess the efficacy of 0.8 mg sustained release pioglitazone, which approximates the 0.6 mg IR dose of our study, for delaying the onset of mild cognitive impairment due to AD in cognitively normal elderly participants (NCT01931566). However, this phase 3 study was prematurely terminated after failing to reach a prespecified efficacy threshold following futility analysis.

Dose selection for any phase 3 program is a nontrivial task that is often done during phase 2 but is particularly difficult for delay-of-onset studies in AD. This is because such studies take several years to complete and often include thousands of participants. Therefore, it becomes impractical to use traditional drug development methods, especially if trying to use multiple dose arms. One alternative to finding a path forward is to identify changes in brain function that are considered key for the target disorder and to use them as a biomarker to monitor how different doses affect changes in that circuit. This study represents part of such an attempt. As this type of dose finding is not well established, it is not entirely clear what the criteria should be for choosing the optimal dose nor is it yet clear what kind of consistency is needed for confidence that the chosen dose is optimal and does not require further verification. Nevertheless, our findings suggest that pharmacologic fMRI may be one avenue forward in trying to answer some of these developmental questions, particularly within delay-of-onset research in AD.

Acknowledgments

The authors gratefully acknowledge the significant contributions of Dr Allen D. Roses in the concept, design, and analysis of this study. Dr Roses passed away before the preparation of this manuscript. The authors additionally

acknowledge the study volunteers and clinic staff for their contributions to this research, and Donna Crenshaw for early discussions on study considerations.
Funding: This work was supported by Takeda Pharmaceutical Company Limited through a research agreement with Duke University. Editorial support was provided by Chameleon Communications International Ltd, UK (a Healthcare Consultancy Group company) and sponsored by Takeda Pharmaceutical Company Ltd.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2019.05.004.

RESEARCH IN CONTEXT

1. Systematic review: Epidemiologic studies report that thiazolidinedione (TZD) use is associated with a reduction in the incidence of dementia. Functional magnetic resonance imaging may support the application of TZDs in dementia treatment by elucidating dose-dependent drug effects on brain activation supporting declarative memory.
2. Interpretation: Compared with placebo, 0.6 mg of the TZD pioglitazone was associated with increased mnemonic hippocampal activity at 7 and 14 days after treatment in healthy elderly volunteers. This drug effect was not apparent at the level of memory performance or at higher doses, which were associated with more nonspecific distributed effects on brain activity.
3. Future directions: The observed effects of 0.6 mg of pioglitazone on mnemonic hippocampal activity could represent one biological mechanism through which TZDs may contribute to reduced incidence of dementia. Additional research is needed to elucidate the nonlinear effects of low-dose pioglitazone on mnemonic hippocampal activity and to evaluate the effects on at-risk individuals.

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