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Measuring brain glucose metabolism in order to predict response to antidepressant or placebo: A randomized clinical trial

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ABSTRACT

There is critical need for a clinically useful tool to predict antidepressant treatment outcome in major depressive disorder (MDD) to reduce suffering and mortality. This analysis sought to build upon previously reported antidepressant treatment efficacy prediction from 2-[^{18}F]-fluorodeoxyglucose - Positron Emission Tomography (FDG-PET) using metabolic rate of glucose uptake (MRGlu) from dynamic FDG-PET imaging with the goal of translation to clinical utility. This investigation is a randomized, double-blind placebo-controlled trial. All participants were diagnosed with MDD and received an FDG-PET scan before randomization and after treatment. Hamilton Depression Rating Scale (HDRS-17) was completed in participants diagnosed with MDD before and after 8 weeks of escitalopram, or placebo. MRGlu (mg/(min*100 ml)) was estimated within the raphe nuclei, right insula, and left ventral Prefrontal Cortex in 63 individuals. Linear regression was used to examine the association between pretreatment MRGlu and percent decrease in HDRS-17. Additionally, the association between percent decrease in HDRS-17 and percent change in MRGlu between pretreatment scan and post-treatment scan was examined. Covariates were treatment type (SSRI/placebo), handedness, sex, and age. Depression severity decrease (n = 63) was not significantly associated with pretreatment MRGlu in the raphe nuclei (β = -2.61e^{-03} [-0.26, 0.25], p = 0.98), right insula (β = 0.05 [-0.23, 0.32], p = 0.72), or ventral prefrontal cortex (β = 0.06 [-0.23, 0.34], p = 0.68) where β is the standardized estimated coefficient, with a 95% confidence interval, or in whole brain voxelwise analysis (family-wise error correction, alpha = 0.05). MRGlu percent change was not significantly associated with depression severity decrease (n = 58) before multiple comparison correction in the RN (β = 0.20 [-0.07, 0.47], p = 0.15), right insula (β = 0.24 [-0.03, 0.51], p = 0.08), or vPFC (β = 0.22 [-0.06, 0.50], p = 0.12). We propose that FDG-PET imaging does not indicate a clinically relevant biomarker of escitalopram or placebo treatment response in heterogeneous major depressive disorder cohorts. Future directions include focusing on potential biologically-based subtypes of major depressive disorder by implementing biomarker stratified designs.

1. Introduction

Over 11 million adults experienced severe impairment due to MDD in 2017 (Ettman et al., 2020). Despite this considerable impact on patient wellbeing and productivity, there are currently no objective tools to guide clinicians in choosing antidepressant treatments. To avoid

Abbreviations: MDD, major depressive disorder; SSRIs, selective serotonin reuptake inhibitors; PET, Positron Emission Tomography; FDG, 2-[^{18}F]-fluorodeoxyglucose; FDG-PET, 2-[18F]-fluorodeoxyglucose - Positron Emission Tomography; MRGlu, metabolic rate of glucose uptake; vPFC, ventral prefrontal cortex; RN, raphe nuclei; SCID-IV, structured clinical interview for diagnosis; MADRS, Montgomery–Åsberg Depression Rating Scale; HDRS-17, Hamilton Depression Rating Scale; 5-HT$_{1A}$, serotonin 1A receptor; SimE, Simultaneous Estimation.

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ineffective treatment trials, expedite remission, and thus decrease suffering, there is a need for a clinically useful pretreatment predictive marker of an individual's course of illness. An objective predictive marker could identify patients' likelihood to remit following the most commonly used monotherapy for MDD, SSRIs (Leuchter et al., 2008). This has been a targeted focus of neuroimaging studies including PET studies.

Among PET investigations, there have been at least seven studies (Brody et al., 1999; Buchsbaum et al., 1997; Konarski et al., 2009; Little et al., 2005; Mayberg et al., 1997; McGrath et al., 2013; Milak et al., 2009) targeting a pretreatment marker of antidepressant efficacy through the use of resting state FDG-PET imaging (Table 1). The most notable of the pretreatment prediction studies was conducted by McGrath et al. in 2013, which prompted Dr. Thomas Insel, former National Institute of Mental Health director, to state that FDG-PET was 'on the cusp' of clinical utility for treatment guidance (Asher, 2013). This study identified higher pretreatment right insula metabolism to be associated with reduction of symptom severity specifically with SSRI treatment. Despite this seminal work and other well-done investigations, FDG-PET has yet to be clinically translated as a technique to predict treatment outcome for MDD patients in the clinic. In the present investigation, we sought to develop this technique as a clinically useful measure.

The most rigorous application (Boellaard, 2009) of PET imaging involves a dynamic technique with use of blood as a reference for full quantification of metabolic rate, referred to as metabolic rate of glucose uptake, 'MRGlu'. The dynamic technique refers to graphical modeling of FDG uptake from regional activity over time for metabolic rate of glucose quantification (Rahmim et al., 2019). In the present investigation, we applied this dynamic technique through a randomized, double-blind placebo-controlled trial of the SSRI escitalopram with 63 currently depressed participants. Only one (Little et al., 2005) of the seven (Brody et al., 1999; Buchsbaum et al., 1997; Konarski et al., 2009; Little et al., 2005; Mayberg et al., 1997; McGrath et al., 2013; Milak et al., 2009) pretreatment studies have applied dynamic technique. In addition, these seven studies have been highly variable in methods, potentially explaining the lack of translation of this technique to clinical utility (Knudsen et al., 2020). We hypothesize that the predictive insula metabolism signal in the SSRI group determined in McGrath et al 2013 will be enhanced through application of dynamic PET imaging technique with blood as a reference. In combination with results from previous FDG-PET investigations, we also hypothesize that pretreatment MRGlu in the left vPFC (Buchsbaum et al., 1997; Little et al., 2005; Mayberg et al., 1997) and the RN (Milak et al., 2009) will be associated with post-treatment depression severity decrease (referred to as *prediction study*).

While these regions were primarily chosen because of the confluence of data from previous studies indicating their predictive potential, there is also evidence to suggest that these regions are biologically relevant to depression severity decrease. We have shown in previous investigations that high pretreatment raphe nuclei (RN) 5-HT_{1A} density is associated with MDD remission (Miller et al., 2013). Serotonergic neurons from the RN project throughout the brain. Activation of 5-HT_{1A} receptors induces hyperpolarization of these serotonergic neurons, thus inhibiting firing of neuronal action potentials (Kaufman et al., 2016), resulting in lower metabolic demand in the RN (Kaufman et al., 2016). This finding is therefore consistent with our previous FDG study showing antidepressant remitters have lower pretreatment RN FDG uptake (Milak et al., 2009). Additionally, insula activity has been associated with interoception, and emotional self-awareness including integration of visceral perception (McGrath et al., 2013) and the vPFC has been implicated in playing a role in regulating negative emotion, specifically through its functional connectivity with the amygdala and anterior cingulate cortex (Hiser and Koenigs, 2018).

Additionally, change in glucose metabolism assessed by FDG-PET between pretreatment and post-treatment may be clinically meaningful: it is of interest to determine if potential regional activity change as indicated by FDG-PET is associated with symptom abatement over the course of treatment because this may direct the development of regionally targeted interventions to alleviate symptoms. Specifically, FDG-PET metabolism difference in the insula (Brody et al., 2001; Kennedy et al., 2001) and left vPFC (Brody et al., 1999; Brody et al., 2001; Kennedy et al., 2001) over the course of treatment has been indicated in previous literature (Table 2). With an additional PET image following

Table 1
Prediction study review. Review of studies demonstrating regional predictive signal such that either lower or higher estimates of pretreatment metabolism is associated with decrease in depression severity. This table is divided into 'Hypothesized regions relevant to present prediction study', which demonstrates outcomes specific to our regions of interest, the insula and vPFC, and 'Other regions previously indicated as predictive', which demonstrates the variability in similar past investigations. Abbreviations: Anterior cingulate cortex (ACC), cognitive behavioral therapy (CBT), dorsolateral prefrontal cortex (DLPFC), electroconvulsive therapy (ECT), Major Depressive Disorder (MDD), prefrontal cortex (PFC), selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), ventral prefrontal cortex (vPFC).

Author	N, MDD	Treatment	FDG Outcome Measure	Hypothesized regions relevant to present prediction study		Other regions previously indicated as predictive
				Insula	vPFC	
(Mayberg et al., 1997)	18	SSRI (n = 13), TCA or Bupropion (n = 5)	Relative cerebral metabolic rate for glucose	**Lower**	**Lower**	**Lower:** DLPFC, premotor cortex **Higher:** rostral ACC
(Brody et al., 1999)	16	Paroxetine	Normalized metabolic values	–	–	**Lower:** left ventral ACC
(Milak et al., 2009)	33	Paroxetine, followed by either another SSRI alone or in combination with non-selective monoamine reuptake inhibitor (n = 20),ECT, or an antidepressant other than paroxetine (n = 13)	Relative regional cerebral metabolic rate	–	–	**Lower:** midbrain including Raphe Nuclei
(McGrath et al., 2013)	63	CBT (n = 33), Escitalopram (n = 30)	Relative glucose metabolic rates	**Lower:** insula with CBT. **Higher:** insula with SSRI. Right anterior insula most robust.	–	–
(Buchsbaum et al., 1997)	17	Placebo (n = 10), Sertraline (n = 7)	Relative metabolic rate	–	**Higher:** Sertraline	–
(Little et al., 2005)	20	Bupropion or Venlafaxine. Crossed over either treatment (n = 14)	**Dynamic, Quantitative** regional cerebral glucose metabolic rate	**Lower**	**Lower**	**Lower:** left medial PFC, left amygdala and parahippocampal regions
(Konarski et al., 2009)	24	CBT (n = 12), Venlafaxine (n = 12)	Relative regional glucose metabolism	–	–	**Lower:** ventral ACC

Table 2
Pre/post study review. Review of studies demonstrating change in estimates of metabolism between pretreatment scan and post-treatment scan in either all participants, participants with MDD that responded to treatment, or participants given sertraline, but not placebo. This table is divided into 'Hypothesized regions relevant to present Pre/post study', which demonstrates outcomes specific to our regions of interest, the insula and vPFC, and 'Other regions previously indicated as having change in estimates of metabolism in Pre/post study', which demonstrates the variability in similar past investigations. Abbreviations: Anterior cingulate cortex (ACC), cognitive behavioral therapy (CBT), dorsolateral prefrontal cortex (DLPFC), major depressive disorder (MDD), orbitofrontal cortex (OFC), prefrontal cortex (PFC), ventral prefrontal cortex (vPFC).

Author	N, MDD Completing the study	Treatment	FDG Outcome Measure	Participant Category	Hypothesized regions relevant to present Pre/post study		Other regions previously indicated as having change in estimates of metabolism in Pre/post study
					Insula	vPFC	
(Buchsbaum et al., 1997)	17	Placebo (n = 10) Sertraline (n = 7)	Relative metabolic rate	MDD treated with sertraline	–	–	**Increased**: right parietal lobe and left occipital lobe **Decreased**: right occipital lobe
(Brody et al., 1999)	16	Paroxetine	Normalized metabolic values	MDD Responders	–	**Decreased**	**Decreased**: OFC
(Brody et al., 2001)	24	Paroxetine (n = 10), interpersonal psychotherapy (n = 14)	Normalized metabolic values	MDD regardless of outcome	**Increased**	**Decreased**	**Decreased**: DLPFC and ACC **Increased**: left temporal lobe
(Kennedy et al., 2001)	13	Paroxetine	Relative Regional Brain Glucose Metabolism	MDD regardless of outcome	**Decreased**	**Increased**	**Increased**: DLPFC, medial PFC and dorsal ACC **Decreased**: anterior, right hippocampus and parahippocampus
(Kennedy et al., 2007)	24	CBT (n = 12), Venlafaxine (n = 12)	Relative metabolic rate	MDD Responders	–	–	**Decreased**: OFC and right dorsomedial PFC **Increased**: right occipital-temporal cortex

treatment, we also analyze the association between MRGlu percent change and depression severity decrease over treatment (referred to as *pre/post study*).

Establishing a clinically useful pretreatment predictive marker of an individual's course of illness is imperative to decrease the disease burden of MDD. Given that FDG is relatively inexpensive and widely used clinically for diagnosis and monitoring conditions such as cancers (Ziai et al., 2016), the present investigation brings relevant and impactful information to the field. This study aims to assess clinical translatability of FDG-PET imaging as a means of predicting antidepressant treatment efficacy.

2. Materials and methods

2.1. Participant population

The Institutional Review Board of Stony Brook University approved this study. All participants signed informed consent after receiving a complete description of the study, were at least 18 years of age and were recruited as a community sample that responded to an ad in this single center investigation. All participants were diagnosed with current MDD verified by trained rater with the SCID-IV (First et al., 2002) and a score of 22 or higher on the MADRS (Montgomery and Asberg, 1979). A score of 22 or higher on the MADRS was chosen for inclusion because it has been used in multiple clinical trials to define moderate depression (Gorwood et al., 2007; Iqbal and Mathew, 2020). Potential participants were excluded under the following conditions: successful current antidepressant treatment, medical contraindications to escitalopram including previous failure of escitalopram therapy, electroconvulsive therapy within 6 months, psychotic disorders (past or current), psychotic symptoms (current), past diagnosis of bipolar disorder, actively suicidal, high potential for excessive substance use during the study period, significant active physical illness, significant neurological deficits, and contraindications to MRI or PET imaging including pregnancy or breast feeding. High potential for excessive substance use was decided by the clinician in conjunction with the study team on an individual basis with reference to the participant's clinical interview, lifestyle, frequency of current substance use, protective factors and other related information. Handedness was recorded with the Edinburgh Handedness Inventory (Oldfield, 1971).

Sample size was determined by power analysis to detect a true correlation as low as 0.39, with 80% power (two-tailed analysis, alpha = 0.05). 613 individuals completed phone screens, 211 signed consent, of whom 125 were eligible and interested (CONSORT diagram, supplemental). Participants signed full protocol consent before a clinical evaluation was performed to assess exclusion criteria such as presence of bipolar disorder, psychotic symptoms, or indications that the participant was actively suicidal. 85 participants completed pretreatment scan and then were randomized. Seven completed pretreatment scans but did not complete the full course of treatment (lost to follow-up) and were dropped from the study. Three participants were excluded from analysis due to excessive motion or instrument error at pretreatment scan. Additionally, eleven participants with>20% blood glucose change between pre-scan and post-scan sampling were also excluded due to limitations of kinetic FDG uptake modeling, which has decreased accuracy with fluctuating blood glucose over the course of the scan (Bartlett, 2019; Dunn et al., 2009). Adding in these 11 participants did not alter significance of linear regressions in the *prediction* or *pre/post study*. One participant was dropped due to diabetes, given that abnormalities in insulin response influence blood sugar concentration, which can affect FDG uptake modeling (Dunn et al., 2009). 63 participants are included in the *prediction study* but only 58 are included in the *pre/post study* due to failure to complete post-treatment scan (3), uncorrectable image motion in post scan (1), and>20% blood glucose change during the post scan (1). Sample characteristics are described in Table 3 and Table 4, as

Table 3
Participant demographics. Non remitters (Non-Rem.) and remitters (Rem.) are compared using a chi-square test.

	Non-Remitter		Remitter		p-value for group difference between remitters and non-remitters
	n	% of Non-Rem.	n	% of Rem.	
Total	42	–	21	–	p = 0.10
Female	29	69	10	48	
Caucasian	26	62	12	57	p = 0.72
Not Caucasian	16	38	9	43	
Medication naïve	20	50	6	30	p = 0.14
History of psychotropic medication	20	50	14	70	

Table 4
Participant treatment profile. Non-remitters and remitters are compared using independent two-sample *t*-test ([a] significant, $p < 0.05$). Abbreviations: Major depressive disorder (MDD), Hamilton Depression Rating Scale −17 (HDRS-17).

	Non-Remitter mean	SD	Remitter mean	SD	p value for group difference between remitters and non-remitters
Age (years)	29.92	13.33	28.45	14.93	$p = 0.71$
Age of MDD onset (years)	23.02	23.36	21.81	20.75	$p = 0.83$
Maximum Treatment Dose given in Study (either escitalopram or placebo, mg)	29.52	3.09	28.10	6.8	$p = 0.37$
Pretreatment HDRS-17	18.57	5.61	16.00	3.24	$p = 0.02$[a]
Post-treatment HDRS-17	13.86	5.22	4.05	2.18	$p < 0.01$[a]

divided by remitters and non-remitters. Remission was defined a priori as post-treatment HDRS-17 less than or equal to 7 (McGrath et al., 2013) and a depression severity decrease of at least 50% (Milak et al., 2009). Non-remission is defined as not meeting these criteria. HDRS-17 was used in order to maintain consistency with preceding studies of FDG-PET use in remission prediction (McGrath et al., 2013; Milak et al., 2009) enabling a direct comparison in participant populations.

2.2. Treatment

Participants were either medication naïve or medication free for 3 weeks after completing ineffective psychotropic medication washout before study initiation. Washout was completed over a maximum of 4 weeks before the 3-week psychotropic medication free period. Participants were randomized through a parallel, double-blind design to treatment with either placebo or escitalopram after pretreatment scan. Group allocation for all participants was determined at study initiation by pseudo-random allocation scheme (1:1 ratio) generated by the pharmacist with the software Research Randomizer (http://www.randomizer.org/). Bottle labelling and medication distribution was completed by the pharmacist, allowing for a double-blind design. Participants met with the study clinician in person each week for the first four weeks, and every other week for the following month. The maximum dosage of medication was 30 mg (3 pills of SSRI or placebo), with a ramp-up period of dosage in intervals of 10 mg (1 pill SSRI or placebo). Specifically, the participants in the treatment arm received 10 mg of escitalopram in week 1, 20 mg in week 2 and 3, and 30 mg in weeks 4–8. This scheduled was altered in the event of treatment intolerance such that titration was increased at a lower rate, maintained, or the dose was decreased. The HDRS-17 was administered prior to pretreatment imaging and after ~ 8 weeks of treatment, prior to unblinding. The percent decrease between pretreatment and post-treatment HDRS-17 (depression severity decrease) was used as the primary outcome measure. The MADRS (used for inclusion) was not used as an outcome measure in order to maintain independence of symptom rating from inclusion criteria. Through this design, we sought to avoid inflation of symptoms and artificial treatment response. Following unblinding, participants in the placebo group were offered open treatment, and those on escitalopram were offered to continue escitalopram if successful or open treatment if not.

2.3. Imaging acquisition, reconstruction, and pre-processing

2.3.1. PET processing

Up to 185 MBq of 2-[18F]-fluorodeoxyglucose (FDG) were injected intravenously and emission data was acquired for 60 min on a Siemens Biograph mMR. Raw listmode PET data were reconstructed offline using Siemens' e7 Tools software and a CT-like Boston MR-based attenuation map (Izquierdo-Garcia et al., 2014; Ladefoged et al., 2017). Sinogram files were generated using the following frame definitions: 8x15sec, 6x30sec, 5x60sec, 4x300sec, and 3x600sec. Sinogram data were back-projected with filtering onto a 344x344 matrix with scatter correction and no smoothing. Participant motion was corrected by rigid body registration to a reference frame (Pillai et al., 2018) with subsequent coregistration of MRI to the average PET image.

2.3.2. MRI processing

The insula and vPFC were automatically delineated on the participant's MRI using atlases as previously described (Milak et al., 2010). For voxel analysis and RN delineation (see below, 2.3.3), each participant's MRI was registered to MNI space using Advanced Normalization Tools (Avants et al., 2011). The high resolution MNI template in which the RN was delineated was then registered to subject scan to bring this region into subject space, such that all regions for the region-based analysis were delineated in individual subject space.

2.3.3. RN delineation

RN delineation was performed using an atlas generated by our group (https://renaissance.stonybrookmedicine.edu/psychiatry/research/cubit/data) and is publicly available at this website and upon request. This RN atlas, in MNI space, was created from parametric 5-HT_{1A} average binding potential maps generated with the 5-HT_{1A} tracer [^{11}C]-WAY100635. These maps were then thresholded in the midbrain (Pillai et al., 2018).

2.4. Dynamic analysis

The dynamic technique allows for quantification of MRGlu by modeling FDG uptake and radioactivity in the blood. Average emission activity within each region was calculated per each frame to create the time activity curve. MRGlu was estimated from the time activity curve via the Patlak graphical approach, correcting for blood glucose (blood glucose was averaged from manual blood sampling before and after scanning) and the lumped constant, using an arterial input function recovered via SimE. Traditionally, dynamic and quantitative FDG imaging requires an arterial input function, and thus arterial catheterization, to quantify MRGlu in each brain region. SimE is a mathematical method of calculating the most likely arterial input function by only using one venous blood sample taken after injection of tracer. This technique has been validated and reported on by multiple publications (Bartlett, 2019; Bartlett et al., 2019; Ogden et al., 2010; Zanderigo et al., 2010). In brief, SimE fits kinetic models to multiple brain regions of varying kinetics simultaneously and optimizes the estimation of the arterial input function that is common to these regions. The late-scan plasma sample anchors this arterial input function to constrain the range of possible SimE solutions. As previously validated, venous concentrations of FDG are within 5% of arterial concentration after 40 min (Bartlett, 2019; Chen et al., 1998; Wakita et al., 2000) and therefore, can accurately be used as the SimE anchor (Bartlett et al., 2019). After the initial run of SimE, the initial imputed plasma and outcome values were used in this work. A single venous plasma sample was acquired at a target time of 40 min (range: 39–43.7 min post injection, 3 participants: 63–75 min, 2 participants: arterial sample at 60 min) and used to anchor the generated arterial input function. Most participants underwent two venous blood draws during the scan (around 40 and 60 min post injection). Reliance on the later venous blood draw for SimE (63–75 min) occurred only when the 40 min sample was not available, for example if there were difficulties in obtaining the blood draw near the 40 min time slot.

2.5. Statistical Analysis

For all statistical tests, alpha was set at 0.05.

2.5.1. Prediction study

Linear regression was used to examine the association between pretreatment MRGlu and depression severity decrease ([(pre-treatment HDRS-17 - post-treatment HDRS-17) / pretreatment HDRS-17] * 100). Pretreatment MRGlu was assessed in the 3 regions: RN, right insula, and left vPFC. Treatment type (SSRI or placebo), handedness (continuous variable), sex, and age were covariates.

2.5.2. Pre/post study

Linear regression was used to examine the association between MRGlu percent change ([(post-treatment MRGlu - pretreatment MRGlu) / pretreatment MRGlu] * 100) and depression severity decrease. MRGlu percent change was assessed in the 3 regions: RN, right insula, and left vPFC. Treatment type (SSRI or placebo), handedness (continuous variable), sex and age were covariates.

2.6. Image processing for dynamic voxelwise analysis

Voxel maps of MRGlu were generated from the motion corrected co-registered images. MRGlu was calculated by application of the Patlak equation to the time activity curve of each voxel using arterial input function calculated during the regional analysis by SimE. Voxel maps (generated in subject PET space) were warped to MNI standard space using the transformation described above (MRI Processing, 2.3.2) and then smoothed with 8 mm Gaussian kernel. Voxelwise significant cluster analysis was performed using SPM8; Wellcome Trust Centre for Neuroimaging, (http://www.fil.ion.ucl.ac.uk/spm/). A full factorial design with one level was used to assess the relationship between pretreatment MRGlu and depression severity decrease while covarying for age, sex, handedness and treatment type. Family-wise error correction was applied (alpha = 0.05) and extent threshold of 50 voxels.

2.7. Relative measures comparison

In order to make direct comparison to McGrath et al's 2013 study, we replicated their technique as closely as possible (McGrath et al., 2013). The two groups for comparison in that analysis were remitters and non-responders to escitalopram. We followed McGrath's inclusion criteria to include only participants with a pretreatment HDRS-17 of 15 or higher and defined remitters as attaining a post treatment HDRS-17 less than or equal to 7. Mirroring McGrath, we compared remitters to non-responders, defined as those attaining a decrease in HDRS-17 score of 30% or less. Partial responders were defined by a>30% decrease in HDRS-17 score but this cohort did not meet criteria for remission.

We averaged the last two 10-minute motion corrected co-registered PET frames, divided by injected dose and mean image intensity for generation of static relative glucose metabolic rate emission images. Static voxel images were smoothed with 8 mm Gaussian kernel and then warped to MNI standard space using the transformation described above (MRI Processing). Voxelwise significant cluster analysis was performed using SPM8 with a statistical design of a two-sample *t*-test for group comparison (remitters, non-responders) of pretreatment scan among participants who were randomized to escitalopram. No covariates were used. Family-wise error correction was applied (alpha = 0.05) and extent threshold of 50 voxels.

3. Results

3.1. Participants

End of trial enrollment was determined by meeting recruitment goals. See Tables 3 and 4. Of the 63 participants included in the *prediction study*, 29 had been prescribed at least one psychotropic medication. Three of the 29 participants did not provide further details of medication history. 22 participants were prescribed at least an SSRI. Of these individuals, six were only prescribed SSRI's. Ten participants had a medication history of an SSRI and at least another class of antidepressants. Only one individual took a psychotropic medication (stimulant) without a history of antidepressant use. In the 29 participants with history of psychotropic medications, the following medications other than antidepressants were reported: stimulants (n = 5), atypical antipsychotic (n = 3), benzodiazepine (n = 2), buspirone (n = 2), opioids (n = 2), lithium (n = 1) and an anticonvulsant (n = 1). Recruitment began 3/20/2015 and follow-up on the last subject was completed on 3/04/2020.

3.2. Prediction study

Depression severity decrease was not significantly associated with pretreatment MRGlu (n = 63) before multiple comparison correction in the RN (β = -2.61e^{-03} [-0.26, 0.25], p = 0.98), right insula (β = 0.05 [-0.23, 0.32], p = 0.72), or vPFC (β = 0.06 [-0.23, 0.34], p = 0.68) where β is the standardized estimated coefficient, and the 95% confidence interval is reported (Fig. 1A). Covariates of treatment type, handedness, sex and age were not significantly associated with depression severity decrease after multiple comparisons correction ($p > 0.05$). Fig. 1 divides remitters from non-remitters along the × axis for visual comparison of outcome measure along the y-axis, although remission was not an aspect of statistical comparison. Of those that received placebo, 13 out of 32 participants achieved remission. Of those that received escitalopram, 8 out of 31 participants achieved remission. As determined with a chi square test, the difference in remission rates was not significant (χ = 1.56, p = 0.21).

3.3. Pre/post study

MRGlu percent change was not significantly associated with depression severity decrease (n = 58) before multiple comparison correction in the RN (β = 0.20 [-0.07, 0.47], p = 0.15), right insula (β = 0.24 [-0.03, 0.51], p = 0.08), or vPFC (β = 0.22 [-0.06, 0.50], p = 0.12) (Fig. 1B). Covariates of treatment type, handedness and age were not significantly associated with depression severity decrease ($p > 0.05$) after multiple comparisons correction. Male sex, relative to female sex, was related to more decrease in depression severity over the course of the study ($p < 0.05$, after correcting for multiple comparisons).

3.4. Dynamic voxelwise analysis

There were no significant voxel clusters indicating the association between depression severity decrease and pretreatment MRGlu at an alpha = 0.05 after adjusting for family-wise error while covarying for age, sex, handedness and treatment type.

3.5. Relative measures comparison

Between remitter (n = 6) and non-responder (n = 11) images of relative glucose metabolic rate acquired pretreatment, there were no significantly different clusters of voxels.

3.6. Analysis with only medication naïve participants

In a post-hoc analysis, the regional prediction hypotheses were tested with only medication naïve participants (n = 34). The results remained unchanged in that MRGlu percent change was not significantly associated with depression severity decrease in the RN (β = 0.03 [-0.38, 0.43], p = 0.89), right insula (β = -0.03 [-0.48, 0.42], p = 0.90), or vPFC (β = -0.03 [-0.46, 0.41], p = 0.90).

4. Discussion

The present investigation demonstrates that FDG signal alone, analyzed in these ways, is unlikely to be a clinically relevant biomarker

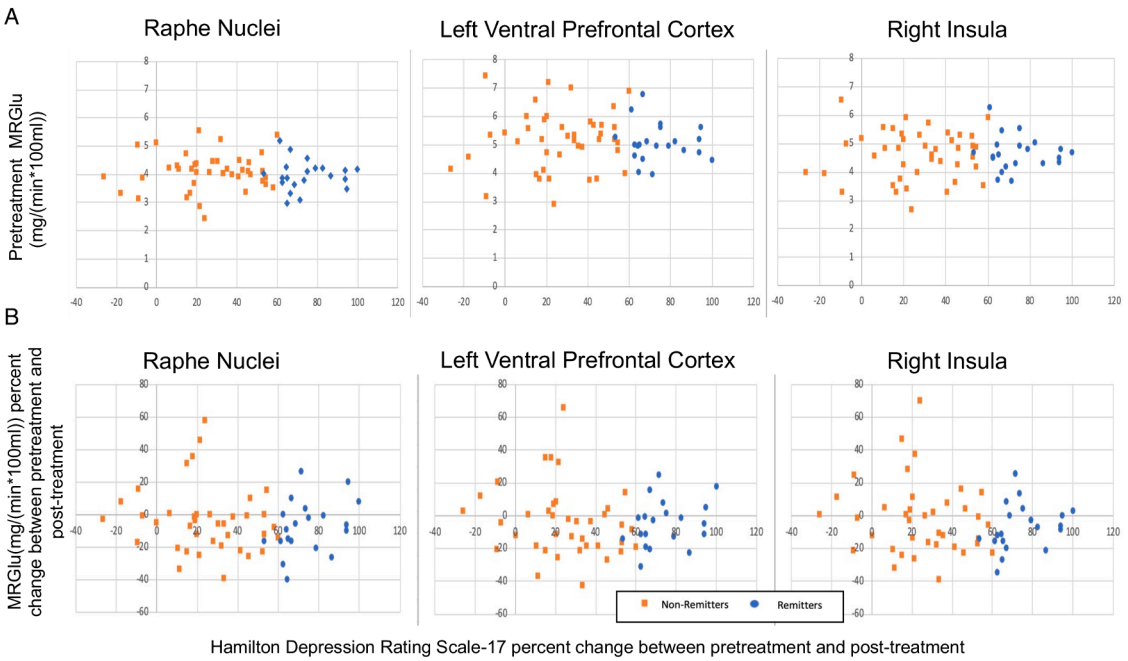

Fig. 1. Association between Hamilton Depression Rating Scale-17 score percent change between pretreatment and post-treatment and (A.) pretreatment metabolic rate of glucose uptake (MRGlu) (mg/(min*100 ml)) and (B) percent change between pretreatment and post-treatment MRGlu (mg/(min*100 ml)) in the raphe nuclei (RN), left ventral prefrontal cortex (vPFC) and right insula. MRGlu values are derived from regional time activity analysis and not from voxel measures. Positive values on the x-axis indicate depression severity decreased with treatment. Negative values indicate that depression severity increased with treatment. Non-remitters (orange) and remitters (blue) are indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of treatment response in MDD that is generalizable to heterogeneous MDD cohorts. This is critical knowledge to allow research time and dollars to be allocated efficiently.

We applied a dynamic technique to calculate MRGlu, in a randomized, double-blind placebo-controlled trial of the SSRI escitalopram. Static imaging techniques generally involve a single PET frame and do not take into account changes in tracer uptake over time. The dynamic technique used in this work differs from a static technique in that it involves modeling of FDG uptake over time and takes into account FDG concentration in plasma and resting plasma blood glucose, allowing absolute quantification of glucose metabolism (Boellaard, 2009; Rahmim et al., 2019) therefore increasing potential for replicability. Given that glucose and oxygen are the only energy sources for the brain under non-starvation conditions, estimation of glucose metabolism with FDG uptake sensitively measures cerebral functioning based on metabolic demand (Baxter et al., 1989). For example, McGrath et al. 2013 describes the specificity of pretreatment insula metabolism to predict response to the SSRI escitalopram, but not to cognitive behavioral therapy (McGrath et al., 2013). Because previous investigations have demonstrated pretreatment regional glucose metabolism differences associated with likelihood to respond to SSRI's, we sought to evaluate this association in the present cohort in order to assess replicability and clinical translation of this predictive technique (Brody et al., 1999; Buchsbaum et al., 1997; Mayberg et al., 1997; McGrath et al., 2013; Milak et al., 2009).

In light of high methodological variability in the literature preceding this study (Table 1), we sought to conduct a rigorous study design. To maintain consistency with preceding studies, HDRS-17 was used (McGrath et al., 2013; Milak et al., 2009). Additionally, because two of the three regions of interest were sided (left vPFC, but not right and right insula but not left), handedness was included as a covariate to account for potential effects of differences in hemispheric dominance (Tandle et al., 2018). All participants were medication free prior to the pretreatment PET scan for at least three weeks. When analyzing participants who were medication naive independently from those who had a history of psychotropic medication, the primary hypothesis results were unchanged (p-values remained > 0.05) (section 3.6). Post scan data processing underwent rigorous quality control methods. Our investigation determined no association between pretreatment right insula, RN and left vPFC and treatment prediction response.

Absence of a predictive signal, and also the lack of association between MRGlu percent change with depression severity decrease after treatment may be caused by limitations of FDG as a predictive tool for antidepressant efficacy in MDD. This conclusion can be drawn given the lack of replicability in findings in the seven similar studies indicated in Table 1. What may underly this limitation could be the broad heterogeneity of MDD cohorts, reflective of the overall MDD clinical population. In fact, there are 1,497 combinations of eligible diagnostic criteria of DSM-IV that can result in an MDD diagnosis (Ostergaard et al., 2011). In addition to heterogeneity of MDD participant characteristics in clinical populations such as symptom combinations, comorbidities and medication history, there is evidence to suggest MDD as a diagnosis is diverse both in presentation characteristics and underlying neurobiology (Holland et al., 2012; Meyer et al., 2020; Ostergaard et al., 2011). Meyer et al's 2020 publication in the Lancet Psychiatry notes that in general, biological measurements fail to accurately discern between healthy controls and individuals within diagnosis categories such as MDD. Additionally, there is evidence of large variability in genetic polymorphisms thought to underpin categories of disorders such as MDD (Meyer et al., 2020), suggesting MDD itself is not biologically a singular entity. This would further support absence of unified, replicable predictive signal within MDD.

Clinically, the heterogeneity of MDD is well understood including variation in risk factors for MDD development (Hoare et al., 2020) and depressive episode relapse (Kennis et al., 2020). One way to address this heterogeneity is by implementing a biomarker stratified design (Holland et al., 2012). Our group is working towards this in our current project which focuses on identifying MDD patients with neuroinflammation as a potential MDD subtype and treating these patients with anti-inflammatory medication (R01MH123093). This model has potential

for expansion to other possible subtypes: neuroimaging investigations are targeting potential biologically based MDD mechanisms including variations in 5-HT_{1A} physiology (Kaufman et al., 2015) and circadian rhythm disruption (Mendoza, 2019).

In a post-hoc analysis (Relative measures comparison, sections 2.7 and 3.5), we employed the same static, relative measures technique of previous investigators (McGrath et al., 2013) and could not replicate the findings. Our cohort had similar participant group numbers: remitters (n = 6) and non-responders (n = 11). Comparatively, McGrath had remitters (n = 11) and non-responders (n = 6). Our cohort also had comparable depression severity: the average participant HDRS-17 score for McGrath's cohort was approximately 19 on average. The average HDRS-17 score in our investigation is 18. However, McGrath's cohort had a higher average age, in early 40′s, while the average age of this cohort was 29, reflecting the large college population from which many participants were recruited. However, if demographic profile influences study results, the overall applicability of findings to patient populations is limited. Non-replication of significant findings in biomedical research is not rare (Parsey, 2018), yet avoidance of research efforts based on non-replicable findings is dependent on publication of negative outcomes (Collins and Tabak, 2014). This further emphasizes the need for rigorous validation of techniques aimed at translation to clinical settings.

4.1. Limitations

Our average age of participants was 29.4 years, reflecting the large college population in our community, which is younger than the average age of previous investigations. However, this age range is reflective of the ideal target population of this study since individuals 18–25 are reported to have the highest prevalence of major depressive episodes (SAMHSA, 2018). Ideally, results collected in adults with a similar range of depression severity scores should be replicable to any adult, non-geriatric, general population with similar depression severity. The *pre/post study* demonstrated that the covariate of sex was significantly associated with outcome in all 3 regions after multiple comparisons correction such that male sex was related to decrease in depression severity. This can be seen as a limitation because this is a reversal of what is seen in the literature: males are less likely to respond to treatment than females, with this effect particularly pronounced with SSRI treatment (Sramek et al., 2016). This suggests that we may be assessing a cohort which is atypical regarding sex-based MDD characteristics, although this difference is not likely clinically meaningful. Additionally, in 3 out of 121 scans, venous blood samples were collected outside of the 40 min target and instead were collected between 63 and 75 min post injection. This is considered a limitation because these three samples have notable timing variability. However this is unlikely to contribute to outcome measure variability because venous samples taken at both 40 and 60 min post injection have been shown to have FDG activity within 5% of that taken from standard arterial sampling (Bartlett, 2019). The analyses were also repeated removing these three participants and the primary hypothesis results were unchanged (p-values remained > 0.05).

5. Conclusion

We propose that FDG-PET does not indicate a clinically relevant biomarker of treatment response fit for heterogeneous MDD cohorts. Focusing on potential biologically based subtypes of MDD may offer a solution to addressing the important need for treatment outcome prediction for MDD.

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6.1. Funding

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6.2. Disclosure

Kathryn Hill reports no financial relationships with commercial interests.

John Gardus reports no financial relationships with commercial interests.

Dr. Bartlett reports no financial relationships with commercial interests.

Dr. Perlman reports no financial relationships with commercial interests.

Dr. Parsey reports no financial relationships with commercial interests

Dr. DeLorenzo reports no financial relationships with commercial interests.

6.3. Clinical Trials Registration

Advancing Personalized Antidepressant Treatment Using PET/MRI, ClinicalTrials.gov, NCT02623205.

7. Data and code availability statements

Data is only to be made available via a request to the Authors. The conditions of such a request include:

- The need for a formal data sharing agreement
- The need for approval from the requesting researcher's local ethics committee
- The need to submit a formal project outline
- Requirements for co-authorship or inclusion in the author byline

CRediT authorship contribution statement

Kathryn R. Hill: Writing – review & editing, Formal analysis. **John D. Gardus:** Writing – original draft, Formal analysis. **Elizabeth A. Bartlett:** Writing – original draft, Formal analysis. **Greg Perlman:** Writing – original draft, Formal analysis. **Ramin V. Parsey:** Conceptualization, Investigation, Writing – review & editing. **Christine DeLorenzo:** Conceptualization, Investigation, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102858.

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