Is ^{18}F-FDG-PET suitable to predict clinical response to the treatment of geriatric depression? A systematic review of PET studies

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Abstract:

Background: Geriatric depression is one of the most common psychiatric disorders in later life. It differs from earlier depression in its presentation, etiology, risk factors, protective factors and outcome. Positron emission tomography (PET) can be used to detect changes in neural circuitry in neuropsychiatric disorders, and several authors have assessed its role in the diagnosis and follow-up of patients with geriatric depression. We reviewed the current evidence on the use of Fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) in geriatric depressed patients to find predictors of treatment response.

Methods: We searched PubMed/MEDLINE, Scopus, Embase, Cochrane Library, CINAHL and the PsycINFO databases to find relevant peer reviewed articles on PET in geriatric depression using the search terms ('PET' OR 'positron emission tomography') AND ('mood' OR 'affective disorder' OR 'affective disorders' OR 'depression' OR 'dysthymia' OR 'seasonal affective disorder').

Results: Eleven articles comprising 128 patients were included. We extracted data on glucose uptake of depressed patients and controls at baseline and after different types of intervention (total sleep deprivation followed by a recovery sleep and treatment with selective serotonin reuptake inhibitors.

Conclusions: ^{18}F-FDG-PET showed significant alterations of glucose uptake in several brain areas, in particular the anterior cingulate cortex, which showed reduced metabolism after treatment, and was a predictor of treatment response.

Keywords: PET, Fluorine-18-fluorodeoxyglucose, Depressive Disorder, aging, Blood Glucose/metabolism.

Introduction

Depression in older adults differs from depression in earlier life by its presentation, etiology, risk and protective factors and outcome (Fiske, Wetherell, and Gatz, 2009). Older patients compared with younger adults present more somatic symptoms, whereas feeling of guilt and loss of sexual function are more prevalent in young people (Hegeman, Kok, van der Mast and Giltay, 2012). Furthermore, antidepressant drugs used effectively on younger people often result in a partial response or a recurrence, when used in geriatric patients (Dew et al., 1997). The possibility of distinguishing patients, who would respond better to antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), from those, who would require another class of antidepressant or a psychotherapy, may have a significant impact on the clinical management of geriatric depressed patients and help avoid potential side effects.

There is growing consensus that an array of brain areas are involved in geriatric depression. Positron Emission Tomography (PET) data in patients with geriatric depression show increases in glucose metabolism in the right subgenual and pregenual anterior cingulate cortices (Sacher et al., 2012). PET is used to detect changes in neural circuitry in different neuropsychiatric conditions, such as cognitive impairment, dementia (Reiman et al., 1996) and Parkinson's disease (Baba and Takeda, 2012), as well as in patients with affective disorders, such as major depressive disorder (MDD) (Sacher et al., 2012) and bipolar disorder (Schneider, DelBello, McNamara, Strakowski, and Adler, 2012). Specifically, fluorine-18-fluorodeoxyglucose PET (^{18}F-FDG-PET) offers the possibility to distinguish eventual responders and non-responders scanned before pharmacotherapy.

The present study aims to review the current evidence on the role of ^{18}F-FDG-PET in the assessment of geriatric depression systematically.

Methods

A literature search of PubMed/MEDLINE, Scopus, Embase, the Cochrane Library, CINAHL and PsycINFO was carried out to find relevant peer reviewed articles on ^{18}F-FDG-PET in geriatric

depression. A search algorithm based on a combination of the terms: a) [‘‘PET’’ OR “positron emission tomography”] AND b) [“mood” OR “affective disorder” OR “affective disorders” OR “depression” OR “dysthymia” OR “seasonal affective disorder”] was used. No early date limit was used and the search was continued until February 2015. To expand our search, reference lists of the retrieved articles were also screened for additional studies.

All studies or subsets of studies investigating ^{18}F-FDG-PET in geriatric depression were eligible for inclusion.

We excluded a) articles not within the field of interest of this review; b) review articles, editorials or letters, comments, conference proceedings; c) case reports or small case series (less than six patients); d) studies with tracers other than ^{18}F-FDG; e) studies with patients aged less than sixty.

Two researchers (MC and FDC) independently reviewed the titles and the abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above.

For each included study, information was collected systematically about the publication (author names, journal, year of publication, country of origin), the patient characteristics (number of depressed patients and controls, mean age, gender, Hamilton Depression Rating Scale [HDRS] (Hamilton, 1960) and Mini Mental State Examination [MMSE] (Folstein, Folstein and McHugh, 1975), methodological aspects of PET (device used, tracer used, injected activity, time between tracer injection and image acquisition, PET acquisition protocol, image analysis), any intervention, PET evaluation post-intervention and other neuroimaging modalities used.

Results

A) Literature search

The literature generated 3893 articles. Eleven articles comprising 128 geriatric patients were included in this systematic review (see Fig.1). No additional studies were found screening the references. The characteristics of the included studies are presented in Tables 1-3.

[Figure 1 near here]

B) Results of the search

- *PET baseline in unmedicated patients*

Kumar et al. (1993) compared eight patients with geriatric depression and eight patients with dementia of Alzheimer type with no treatment with psychotropic drugs at the time of baseline scanning, documenting widespread non-focal decline in glucose metabolism in geriatric depression that did not differ from the hypometabolism documented in the Alzheimer disease group. The authors demonstrated a decrease in cerebral tracer uptake in most neocortical (frontal, parietal, temporal, sensorimotor, and calcarine regions), paralimbic (orbitofrontal, anterior, and posterior cingulate regions), subcortical (caudate and lenticular nuclei) regions of the brain ($p<0.01$) and in the right cerebellum ($p=0.03$).

Smith et al. (2009b) compared cerebral glucose metabolism of 16 depressed patients with no treatment with psychotropic drugs at the time of baseline scanning and 13 controls as a primary outcome. Higher metabolism was observed in patients compared with controls in anterior (right and left superior frontal gyrus) and in posterior cortical brain areas (precuneus and inferior parietal lobule) and in the right cerebellum. Higher cerebral glucose metabolism in controls compared with patients was found in left medial frontal gyrus..

The Supplementary Figure summarizes results of the study by Smith et al (2009b) in patients with no treatment with psychotropic drugs at the time of baseline scanning indicating brain regions with significant increases (in red) or decreases (in blue) in glucose metabolism.

[Table 1 near here]

- *PET after intervention*

a) PET after total sleep deprivation (TSD) and recovery sleep

A total of 34 elderly depressed patients, who met the DSM-IV criteria for MDD, underwent serial PET studies at baseline and after 36 hours of TSD in three different studies (Smith et al., 1999; Smith et al., 2002a; Smith et al., 2009a). Smith et al. (1999) performed a clinical trial where patients were randomized to one of three groups: TSD + paroxetine for two weeks, TSD + placebo for two weeks, paroxetine only. Age- and sex-matched healthy control subjects were recruited, too, and underwent 36 hours of TSD. Three PET scans were performed on consecutive days (i.e. baseline, 24 hours after TSD, after the first night of recovery sleep) in both patients and controls. A 10 mg dose of paroxetine or placebo was given to patients at bedtime before recovery sleep and the following night. The dose was then increased to 20 mg once daily for two weeks. A fourth PET scan was performed on patients after 2 weeks of treatment with paroxetine or placebo. This study found that after TSD the patients demonstrated a decrease from baseline in metabolism in the right anterior cingulate cortex and right medial frontal gyrus. The healthy control group did not demonstrate significant alterations in glucose metabolism after TSD. After recovery sleep, the patients had lower metabolism compared to baseline in the right medial frontal gyrus and in the inferior frontal gyrus bilaterally. In the anterior cingulate gyrus, metabolism was significantly decreased bilaterally. The patients had increased metabolism in the right postcentral gyrus. In the control group, decreases in glucose metabolism between baseline and recovery sleep were observed in the right medial frontal gyrus and the left occipital association cortex.

In a subsequent study, Smith et al. (2002a) performed PET scans in unmedicated patients the morning after TSD and the morning after recovery sleep (patients received one dose of paroxetine 10 mg on the night before recovery sleep). They found a correlation between the results of PET, after TSD and recovery sleep, and clinical improvement measured by HDRS at 12 weeks. Specifically, authors found that the metabolic change in the right cingulate area was correlated with a positive outcome on the HDRS.

In a further study on 16 depressed patients and 9 healthy controls, Smith et al. (2009a) randomised the patients to one of three groups: TSD + paroxetine (paroxetine 10 mg was given on the night before

recovery sleep), TSD + placebo, and paroxetine only. They found that after TSD, metabolism was decreased in the left cerebellum. The metabolism, in left superior and middle frontal gyri, left precuneus, right middle occipital gyri and right cerebellum, was lower after TSD than after recovery sleep.

[Table 2 near here]

b) PET after treatment with SSRI

Most of the studies retrieved evaluated the regional cerebral flow after the administration of an SSRI: three studies used paroxetine (Smith et al., 1999; Smith et al., 2002a; Smith et al., 2009a) and six using citalopram (Smith et al., 2002b; Smith et al., 2009c; Diaconescu et al., 2011; Smith et al., 2011a; Smith et al., 2011b; Marano et al., 2012). Six of these studies had a 12-week follow-up and used a variable dose of drugs depending on the clinical findings. In some studies, magnetic resonance imaging (MRI) was performed before PET for diagnostic purposes, and in order to exclude patients with stroke or tumor.

After two weeks of administration of paroxetine, Smith et al. (1999) found a lower glucose metabolism than at baseline in the right and left anterior cingulate cortex, and in the left superior/medial frontal gyrus. In a further study, Smith et al. (2009a) described decreased metabolic activity in the inferior frontal gyrus bilaterally and right middle temporal gyrus and right lingual gyrus. An increase was found in the right pre-central gyrus.

Six depressed patients and five controls were evaluated by PET after a single administration of citalopram (40 mg intravenous infusion over 60 minutes) and eight-week administration of citalopram (mean dose 30mg) (Smith et al., 2002b). In the single administration condition, greater metabolic decreases in controls than patients were found in the right cortex (middle frontal, fusiform, inferior parietal, precuneus and supramarginal gyrus). Patients showed greater decreases than controls in the left cortex (middle frontal and inferior parietal) and greater increases in the right putamen, bilaterally

in the occipital cortex and in the left cerebellum. After eight weeks of treatment, compared with baseline, reductions were observed in the right anterior cingulate cortex, bilaterally in the superior frontal cortices, right inferior frontal cortex, right superior temporal cortex, left middle temporal cortex, right insula, left post-central cortex, right parahippocampal gyrus and right midbrain. Increases were observed in the right superior and inferior parietal lobules, left occipital cortex, right putamen, right thalamus and left cerebellum (Smith et al., 2002b).

Smith et al. (2009c) evaluated the acute effects of citalopram infusion on cerebral glucose metabolism in depressed older adults and controls and demonstrated differences in cerebral metabolic response between patients and controls. Greater metabolic decreases in the depressed older adults relative to the controls were observed in left frontal cortex, whereas the controls demonstrated greater right anterior cingulate and left posterior metabolic decreases than the depressed older adults. In depressed older adults relative to controls, the cerebral metabolic response to citalopram is reduced in cortico-cortico and cortico-limbic pathways and increased in the left hemisphere (greater decrease inferiorly and increases posterior).

Diaconescu et al. (2011) found alterations in specific brain networks associated with improvement of affective symptoms and cognitive functions during citalopram treatment in geriatric depression. Specifically, in sixteen geriatric depressed patients results showed decreased cerebral metabolism during citalopram treatment in the anterior cingulate gyrus, middle temporal gyrus, precuneus, amygdala, and parahippocampal gyrus. Increased metabolism was found in the putamen, occipital cortex, and cerebellum.

Furthermore, Smith et al. (2011b) documented changes in cerebral glucose metabolism and serotonin transporter occupancy by citalopram in the striatum and thalamus, as well as in cortical (e.g. anterior cingulate, superior and middle frontal, precuneus, and limbic (parahippocampal gyrus in MDD patients.

Last, Marano et al. (2012) studied long-term effects of citalopram treatment on glucose metabolism in geriatric depression by evaluating nine geriatric patients with a PET scan at two-year follow-up. This study is the follow-up of Diaconescu et al. (2011), already discussed above. Approximately 2 years after the initial study both geriatric depressed patients (most of whom were treated and remitted at longitudinal follow-up) and controls showed decreases in glucose metabolism in posterior association cortices implicated in dementia. More extensive increases in metabolism were observed in patients than controls in anterior cortical regions (anterior cingulate and insula). Irrespective of whether patients were in a treated or untreated state at follow-up, the pattern of changes remained similar. Thus, despite the increase in serotonin concentrations produced by the selective serotonin reuptake inhibitor (which may not be sustained over two years), metabolism increased in anterior regions. The change in cerebral glucose metabolism in both groups was observed without significant cognitive decline, based on the global and domain specific cognitive assessments performed in the study, and are also more extensive than the changes in cerebral atrophy observed (Marano et al., 2012).

[Table 3 near here]

- *Prediction of treatment response*

Scores on the HDRS at baseline, after TSD, after recovery sleep and after intervention are systematically reported in Table 3. The most important feature for the prediction of treatment response is the correlation between changes in cerebral glucose metabolism and changes in HDRS from baseline to after treatment. Response is defined as a reduction of at least 50% from baseline on the HDRS.

First, Smith et al. (2002a) found a positive correlation between the change in HDRS scores after 12 weeks of treatment with paroxetine and cerebral glucose metabolism in the right cingulate gyrus and the right uncus. The authors interpreted the positive correlation as a confirmation of the role of the right cingulate gyrus in modifying depressive symptoms.

In a subsequent study, Smith et al. (2011b) described positive correlations between change in HDRS and glucose metabolism in the left cingulate gyrus (BA 24), right pre-central, right medial frontal, right superior, middle and inferior temporal gyri, left fusiform gyrus and precuneus (bilaterally). Negative correlations were observed in the superior parietal lobule (left), inferior parietal lobule (bilaterally) and right cuneus.

Last and different from previously reviewed studies, Marano et al. (2012) documented that increased cerebral metabolism in the insula, not the anterior cingulate, was correlated with less improvement in HDRS score.

Discussion

^{18}F-FDG-PET showed significant differences between controls and geriatric depressed patients, both in baseline conditions and after different types of intervention (TSD followed by a recovery sleep and SSRI treatment). The baseline metabolic increases found in unmedicated depressed subjects compared to healthy controls in anterior (right and left superior frontal gyri) and posterior (precuneus, inferior parietal lobule) cortical regions might represent a compensatory response in areas of cerebral atrophy (Smith et al., 2009b). The difference between Smith et al. (2009b) and the study by Kumar et al. (1993), which documented decreased cortical ^{18}F-FDG metabolism, is likely to be due to the difference in enrolled patients with a high degree of medical comorbidity and cognitive impairment in Kumar et al. (1993).

Treatment with SSRI or TSD resulted in decreased metabolism in anterior cortical and limbic, and increased posterior cortical metabolism in geriatric depression. The metabolic changes after treatment were associated with improvement in depressive symptoms (Smith et al., 1999; Smith et al., 2002a; Smith et al., 2002b; Smith et al., 2009a; Diaconescu et al., 2011). Specifically, the anterior cingulate cortex was found to have a reduced metabolism after treatment and to be a predictor of treatment response (Smith et al., 1999; Diaconescu et al., 2011; Smith et al., 2011b; Marano et al., 2012). We know from previous studies that the anterior cingulate cortex has a crucial role in initiation,

motivation, and goal-directed behaviour, and may therefore play a fundamental role in MDD (Devinsky, Morrell, and Vogt, 1995; Benjamin and Steffens 2011; Alexopoulos, Gunning-Dixon, Latoussakis, Kanellopoulos, and Murphy, 2008).

Regarding the prediction of treatment response, changes in both positive and negative correlations in cortico-cortico and cortico-limbic pathways were found associated with improvement in depressive symptoms. If confirmed from other prospective studies, these interesting results may open new prospects of translation into clinical practice.

This review has some limitations. First, most of the published studies came from the same research group, include a small number of patients and are heterogeneous for treatment and type of data presented. Moreover, most of the studies summarized have a case-control design and a greater risk of bias. Conversely, some others have enrolled patients from clinical trials (Smith et al., 2009a) in a double blind placebo controlled fashion with a smaller risk of bias. Multimodal neuroimaging studies are required to understand the anatomical and functional underpinnings of depression and to build better models of the neural circuitry involved. Research in the geriatric depression can play a fundamental role in understanding the pathophysiology of depression in earlier stages, as well as highlight differences and similarities with the usually co-existent cognitive impairment. Further prospective studies with patients enrolled from naturalistic unselected cohorts are needed to assess the sensitivity and specificity of the method and to substantiate the role of ^{18}F-FDG-PET in geriatric depression.

Author contributions:

All authors provided substantial contributions to 1) conception and design, acquisition, analysis and interpretation of data, 2) drafting the article and revising it critically for important intellectual content and 3) final approval of the version to be published

Conflict of interest:

The authors declare no conflicts of interest

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Table 1: Basic study characteristics of the articles regarding ^{18}F-FDG-PET in geriatric patients with major depressive disorder

Authors	Country	Study Type	Sample Size Patients vs Controls	Mean Age	% Male	MMSE
Kumar et al. (1993)	USA	Case-control	8 vs 8	71.2	25	28.6±1.3
Smith et al.(1999)	USA	Case-control	6 vs 6	70.5	50	29.2±1.3
Smith et al. (2002a)	USA	Open label Trial[1]	12	70.1	25	29.0±1.0
Smith et al. (2002b)	USA	Case-control	6 vs 5	68.8	16.6	NR
Smith et al. (2009a)	USA	RCT	16 vs 9[2]	69	25	29.5±0.9
Smith et al.(2009b)	USA	Case-control	16 vs 13	65.3	37	28.7±1.1
Smith et al.(2009c)	USA	Case-control	16 vs 13	65.3	37	28.6±1.0
Diaconescu et al. (2011)	USA	Case-control	16 vs 14	65.3	37	28.8±1.0
Smith et al. (2011a)	USA	Single blind Placebo controlled	16	65.3	55	28.7±1.1
Smith et al. (2011b)	USA	Open label Trial	7	65	57.1	29.1±1.1
Marano et al. (2012)	USA	Case-control	9 vs 7	68	NR	28.8±1.0

Legend: NR= Not Reported; HDRS= Hamilton Depression Rating Scale; MMSE= Mini Mental State Examination; RCT= Randomized Clinical Trial; [1]Double blind placebo controlled for the first 2 weeks; [2]Age and gender-matched normal comparison subjects

Table 2: Technical aspects of the included studies

Authors	Time between tracer injection* and image acquisition (min)	Intervention	PET evaluation post intervention	Other Neuroimaging modalities
mar et al. (1993)	45	None	No	None
ith et al. (1999)	35	20 mg paroxetine	Yes	None
ith et al. (2002a)	35	20-40 mg paroxetine	Yes	MRI
ith et al. (2002b)	35	20-40 mg citalopram	Yes	MRI
ith et al. (2009a)	35	20-30 mg paroxetine	Yes	None
ith et al. (2009b)	45	None	No	MRI
ith et al. (2009c)	25	40 mg citalopram	Yes	None
conescu et al. (2011)	25	20-40 mg citalopram	Yes	MRI
ith et al. (2011a)	25	20-40 mg citalopram	Yes	None
ith et al. (2011b)	30	20-40 mg citalopram	Yes	MRI
rano et al. (2012)	25	20-40 mg citalopram	Yes	MRI

Legend: MRI = Magnetic Resonance Imaging; *185 MBq 18-FDG

Table 3: Neuropsychiatric evaluation in the included studies

Authors	HDRS version	HDRS baseline	HDRS after total sleep deprivation	HDRS after recovery sleep	HDRS after intervention (2 weeks)	HDRS after intervention (8 or 12 weeks)
Kumar et al. (1993)	HDRS-17	22.0±6	NR	NR	NR	NR
Smith et al. (1999)	HDRS-13	12.2±3.3	8.5±3.0	7.7±3.1	7.2±2.6	4.8±6.2 (12 weeks)
Smith et al. (2002a)	HDRS-13	16.0±3.9	10.4±4.6	10.0±4.6	9.2±4.7	NR
Smith et al. (2002b)	HDRS-24	27.0±2.8	NR	NR	19.8±5.2	3.4±2.7 (12 weeks)
Smith et al. Paroxetine group (2009a)	HDRS-13	15.7±3.4	9.7±2.9	6.3±5.5	5.3±5.5	NR
Smith et al. TSD/Paroxetine group (2009a)	HDRS-13	15.7±3.6	13.6±4.2	14.4±5.0	9.4±3.7	NR
Smith et al. TSD/Placebo group (2009a)	HDRS-13	16.3±4.8	13.0±5.4	10.2±5.4	12.5±7.9	NR
Smith et al. (2009b)	HDRS-24	26.0±3.5	NR	NR	NR	NR
Smith et al. (2009c)	HDRS-24	26.0±3.5	NR	NR	NR	NR
Diaconescu et al. (2011)	HDRS-24	25.6±4.1	NR	NR	NR	8.7±6.1 (8 weeks)

Smith et al. (2011a)	HDRS-24	27.8±3.7	NR	NR	NR	6.6±5.6 (12 weeks)
Smith et al. (2011b)	HDRS-24	20.6±2.7	NR	NR	NR	7.6±6.1 (12 weeks)
Marano et al. (2012)	HDRS-24	25.1±2.7	NR	NR	NR	5.9±4.7 (8 weeks)

Legend: TSD = Total Sleep Deprivation; HDRS = Hamilton Depression Rating Scale; NR=Not Reported.

Figure legend

Fig.1: Flow chart of the search for eligible studies on the role of positron emission tomography in geriatric depression.

Supplementary Figure: The figure summarizes results of the study by Smith et al (2009b) for brain regions exhibiting significant increases (in red) or decreases (in blue) in glucose metabolism in elderly patients affected by Major Depressive Disorder with no treatment with psychotropic drugs at the time of baseline scanning (figure created with MRIcron, Rorden and Brett, 2000). The peaks of the clusters are reported in MNI coordinates.