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Molecular imaging of serotonin degeneration in mild cognitive impairment

Gwenn S. Smith [a,b,*], Frederick S. Barrett [a], Jin Hui Joo [a], Najlla Nassery [c], Alena Savonenko [d], Devin J. Sodums [a], Christopher M. Marano [a], Cynthia A. Munro [a], Jason Brandt [a], Michael A. Kraut [e], Yun Zhou [f], Dean F. Wong [a,f,g,h], Clifford I. Workman [a]

[a] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[b] Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[c] Department of Medicine, Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[d] Department of Pathology (Neuropathology), Johns Hopkins University School of Medicine, Baltimore, MD, United States
[e] Division of Neuroradiology, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[f] Section of High Resolution Brain PET, Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[g] Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[h] Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

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ABSTRACT

Neuropathological and neuroimaging studies have consistently demonstrated degeneration of monoamine systems, especially the serotonin system, in normal aging and Alzheimer's disease. The evidence for degeneration of the serotonin system in mild cognitive impairment is limited. Thus, the goal of the present study was to measure the serotonin transporter *in vivo* in mild cognitive impairment and healthy controls. The serotonin transporter is a selective marker of serotonin terminals and of the integrity of serotonin projections to cortical, subcortical and limbic regions and is found in high concentrations in the serotonergic cell bodies of origin of these projections (raphe nuclei).

Twenty-eight participants with mild cognitive impairment (age 66.6 ± 6.9, 16 males) and 28 healthy, cognitively normal, demographically matched controls (age 66.2 ± 7.1, 15 males) underwent magnetic resonance imaging for measurement of grey matter volumes and high-resolution positron emission tomography with well-established radiotracers for the serotonin transporter and regional cerebral blood flow. Beta-amyloid imaging was performed to evaluate, in combination with the neuropsychological testing, the likelihood of subsequent cognitive decline in the participants with mild cognitive impairment. The following hypotheses were tested: 1) the serotonin transporter would be lower in mild cognitive impairment compared to controls in cortical and limbic regions, 2) in mild cognitive impairment relative to controls, the serotonin transporter would be lower to a greater extent and observed in a more widespread pattern than lower grey matter volumes or lower regional cerebral blood flow and 3) lower cortical and limbic serotonin transporters would be correlated with greater deficits in auditory-verbal and visual-spatial memory in mild cognitive impairment, not in controls. Reduced serotonin transporter availability was observed in mild cognitive impairment compared to controls in cortical and limbic areas typically affected by Alzheimer's disease pathology, as well as in sensory and motor areas, striatum and thalamus that are relatively spared in Alzheimer's disease. The reduction of the serotonin transporter in mild cognitive impairment was greater than grey matter atrophy or reductions in regional cerebral blood flow compared to controls. Lower cortical serotonin transporters were associated with worse performance on tests of auditory-verbal and visual-spatial memory in mild cognitive impairment, not in controls.

The serotonin system may represent an important target for prevention and treatment of MCI, particularly the post-synaptic receptors (5-HT4 and 5-HT6), which may not be as severely affected as presynaptic aspects of the serotonin system, as indicated by the observation of lower serotonin transporters in MCI relative to healthy controls.

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, 5300 Alpha Commons Drive, 4th floor, Baltimore, MD 21224, United States.
E-mail address: gsmith95@jhmi.edu (G.S. Smith).
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1. Introduction

Neuropathological and neuroimaging studies have consistently demonstrated degeneration of monoamine systems, in particular the serotonin system, in normal aging and in Alzheimer's disease (AD; as reviewed by Hirao and Smith, 2014). Neuropathological studies in AD demonstrate neurofibrillary tangles and neuronal loss in the raphe nuclei, the cell bodies of origin of the cortical serotonin projections (Curcio and Kemper, 1984; Mann and Yates, 1983). Lower cortical serotonin levels and metabolites (5-Hydroxyindoleacetic acid), serotonin transporters (SERT), 5-HT2A and 5-HT1A receptors are also observed in post-mortem studies in AD compared to controls (e.g. D'Amato et al., 1983; Thomas et al., 2006; Zweig et al., 1988; Marcusson et al., 1987; Tejani-Butt et al., 1995; Tsang et al., 2003; Palmer et al., 1988; Bowen et al., 1979, 1983). Serotonergic deficits are greater and more widespread than those of other neurotransmitters in AD, including other monoaminergic and cholinergic systems (Palmer et al., 1988; Cross et al., 1986; Baker and Reynolds, 1989; Nazarali and Reynolds, 1992). Neuroimaging studies have demonstrated lower cortical 5-HT2A receptors, globally (Blin et al., 1993) and, in contrast, lower 5-HT1A receptor in a more localized cortical region, medial temporal cortex, in AD compared to controls (Lanctot et al., 2007). Lower cortical and hippocampal 5-HT1A receptor availability was associated with greater cognitive impairment, lower hippocampal glucose metabolism and greater AD neuropathology in AD (Kepe et al., 2006). Two studies of SERT have shown lower SERT in striatal and midbrain regions (to a greater extent in depressed than in non-depressed AD patients) and lower SERT in mesial temporal cortex, respectively, in AD compared to controls (Ouchi et al., 2009; Marner et al., 2012). Thus, post-mortem and neuroimaging studies of the serotonin system in AD are concordant in the demonstration of serotonin system degeneration in AD.

The evidence for degeneration of the serotonin system in mild cognitive impairment (MCI) is limited. As a result, it is not known whether serotonin degeneration occurs in the pre-clinical stages or later in the course of AD. Neuroimaging studies of the serotonin system in MCI have focused on the 5-HT1A and 5-HT2A receptors (Kepe et al., 2006; Truchot et al., 2008; Hasselbalch et al., 2008). Lower 5-HT2A and 5-HT1A receptors in cortical and hippocampal regions, respectively, in MCI compared to controls have been observed in two studies (Hasselbalch et al., 2008; Kepe et al., 2006). In contrast, a third study reported higher cortical and hippocampal 5-HT1A receptors in MCI and lower cortical and hippocampal 5-HT1A receptors in AD (Truchot et al., 2008). SERT has been a limited focus of study in AD and MCI. Neuroimaging of SERT may better elucidate degeneration of the serotonin system because SERT is a more specific marker of serotonin terminals and of the integrity of serotonin projections than are 5-HT1A or 5-HT2A receptors that are located on the terminals of non-serotonergic neurons (Azmitia and Nixon, 2008). Thus, measuring SERT would be more sensitive to changes intrinsic to the serotonin system than measuring 5-HT1A, 5-HT2A or other serotonin receptors that may be up- or down-regulated due to changes in other neurotransmitter systems (e.g. the cholinergic system; Quirion et al., 1985; Quirion and Richard, 1987) or in response to neuropathological processes such as cerebrovascular disease (Elliott et al., 2009). Further investigation of serotonin degeneration, particularly SERT in MCI, would have implications for whether serotonin degeneration may be a downstream effect of AD pathology or may have a causative role, especially regarding cognitive deficits and neuropsychiatric symptoms. Studies in amyloid transgenic mouse models have shown that cortical serotonin degeneration may precede substantial cortical deposition of beta-amyloid, as well as cortical and hippocampal cell loss, and may be observed early in the course of AD pathophysiology (Liu et al., 2008).

SERT is expressed on serotonin cell bodies and axons in the raphe nuclei and on pre-synaptic serotonin terminals (Blakely et al., 1998). Post-mortem autoradiography studies show high SERT concentrations in anterior cingulate, entorhinal and insular cortices and the temporal pole. Other regions of high SERT concentrations include the hippocampal formation (molecular layer and CA3 and external layers of the subiculum), medial caudate, putamen, ventral striatum, thalamus (anterior, medial-dorsal, midline and pulvinar nuclei), and raphe nuclei (Steinbusch, 1981; Varnäs et al., 2004). Thus, based on the neuroanatomy of the serotonin system, higher concentrations of SERT are observed in cortical and limbic regions and the midbrain serotonin cell bodies, that overlap with regions that show AD pathology (beta-amyloid and tau deposition and deficits in cerebral glucose metabolism in early disease (Arnold et al., 1991, Rub et al., 2000, Smith et al., 1992).

The present study measured SERT in participants with MCI and in demographically matched, healthy, cognitively normal comparison subjects using positron emission tomography (PET) and a well-established, selective radiotracer for SERT, [^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-enzonitrile ([^{11}C]-DASB; Wilson et al., 2002). To determine whether the lower SERT in MCI compared to controls was observed in regions in which cerebral atrophy or lower regional cerebral blood flow (as an index of brain function) were seen, grey matter volumes were measured with magnetic resonance imaging (MRI) and regional cerebral blood flow (rCBF) was measured with PET using the radiotracer [^{15}O]-water. Beta-amyloid imaging was performed in MCI using the radiotracer [^{11}C]-PiB to evaluate, in combination with the neuropsychological testing, the likelihood of subsequent cognitive decline.

To determine whether changes in SERT were associated with memory performance, SERT data were correlated with auditory-verbal and visual-spatial memory tests. To complement the voxel-wise analyses used in the study, exploratory factor analyses were performed with the SERT region of interest data to determine whether the two analysis methods would provide converging results. The following hypotheses were tested: 1) that SERT will be lower in cortical (frontal, temporal and parietal association cortices) and limbic (amygdala, hippocampus) brain regions in MCI compared to controls, 2) that independent, exploratory factor analysis would show lower SERT in cortical regions in MCI compared to controls, consistent with the voxel-wise analysis; 3) that reductions in SERT will be greater and more extensive than reductions in grey matter volumes or rCBF in MCI compared to controls, and 4) that lower cortical and limbic SERT will be associated with greater memory impairment in MCI.

2. Materials and methods

2.1. Subject screening and selection

Participants were recruited from advertisements in the community or from the Johns Hopkins University Alzheimer's Disease Research Center (2P50AG005146). All subjects underwent psychiatric and cognitive evaluations, including a structured clinical interview by a clinical psychologist (SCID), clinical dementia rating scale (CDR), Mini Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI; First et al., 1995; Morris, 1993; Folstein et al., 1976; Cummings et al., 1994). All participants underwent a physical and neurological examination, laboratory testing (including complete blood count and blood chemistries), toxicology screening (psychotropic drugs and drugs of abuse) and MR imaging prior to the PET scans. Participants were excluded from the study who had a history of or active neurological or Axis I psychiatric disorders including substance abuse, who were not medically stable (i.e. if they had poorly controlled hypertension and/or insulin dependent diabetes), for a positive toxicology screening for psychotropic drugs or medications with central nervous system effects or if they used prescription or over-the-counter medications with potential central nervous system effects (e.g. antihistamines, cold medications) within the past two weeks prior to enrollment. The MCIs were required to have a CDR global score of 0.5, whereas the controls were required to have a CDR global score of 0 (normal). Twenty-eight participants with MCI and 28 healthy controls were enrolled. One of the controls and