HHS Public Access

Author manuscript

Neurosci Biobehav Rev. Author manuscript; available in PMC 2016 March 24.

Published in final edited form as:

Neurosci Biobehav Rev. 2015 February ; 49: 157–170. doi:10.1016/j.neubiorev.2014.11.010.

Molecular Imaging of Neuropsychiatric Symptoms in Alzheimer's and Parkinson's disease

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Abstract

Neuropsychiatric symptoms (NPS) are very common in neurodegenerative diseases and are a major contributor to disability and caregiver burden. There is accumulating evidence that NPS may be a prodrome of neurodegenerative diseases and are associated with functional decline. The medications used to treat these symptoms in younger patients are not very effective in patients with neurodegenerative disease and may have serious side effects. An understanding of the neurobiology of NPS is critical for the development of more effective intervention strategies. Targeting these symptoms may also have implications for prevention of cognitive or motor decline. Molecular brain imaging represents a bridge between basic and clinical observations and provides many opportunities for translation from animal models and human post-mortem studies to *in vivo* human studies. Molecular brain imaging studies in Alzheimer's disease (AD) and Parkinson's disease (PD) are reviewed with a primary focus on positron emission tomography studies of NPS. Future directions for the field of molecular imaging in AD and PD to understand the neurobiology of NPS will be discussed.

Keywords

positron emission tomography; molecular imaging; serotonin; dopamine; acetylcholine; Alzheimer's disease; Parkinson's disease; neuropsychiatric symptoms

1. Introduction

Neuropsychiatric symptoms (NPS) occur in the majority of individuals with neurodegenerative diseases (Steinberg et al., 2004; Aalten et al., 2005; Chaudhuri et al., 2006; Geda et al., 2013) and are associated with accelerated cognitive and functional decline, poorer quality of life, earlier institutionalization, and accelerated mortality (Rabins

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et al, 2006). The clinical management of NPS in neurodegenerative diseases is one of the major challenges in geriatric neuropsychiatry. The development of molecular brain imaging methods over the past three decades has had a significant impact on our ability to test neurobiological hypotheses of neuropsychiatric disorders based on an integration of clinical observations, preclinical data (including animal models) and post-mortem data in the living human brain. This review will focus primarily on the molecular imaging studies that have investigated the neurobiology of NPS in Alzheimer's disease (AD) and Parkinson's disease (PD). The available data on mechanism of cognitive impairment that might be associated with NPS will be presented. First, the neural circuitry will be described using measures of cerebral blood flow and metabolism, followed by neurochemical and neuropathological mechanisms based on studies of selective radiotracers. While structural grey and white matter changes associated with NPS have been demonstrated with magnetic resonance imaging (MRI; e.g. Donovan et al., 2013; Kandiah et al., 2014; Kostic and Filippi, 2011; Tighe et al., 2012), the present review will focus on molecular imaging as the data provided might more directly inform treatment development.

2. Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease associated with progressive deficits in verbal and visuospatial memory, as well as other domains of cognition (e.g. executive function). The hallmark pathology involves the accumulation of beta-amyloid plaques and neurofibrillary tangles, as well as neurochemical deficits and other neuropathological processes, including inflammation (as reviewed by Delacourte et al., 1999; Albert, 2011; Nelson et al., 2012). After summarizing the field of the pharmacologic management of NPS in AD, the following sections will review the post-mortem and positron emission tomography (PET) molecular imaging studies of neurochemical deficits in AD and the available data potentially related to mechanisms of NPS including anxiety, depression, apathy and psychotic symptoms.

2.1 The treatment of NPS in Alzheimer's disease

Epidemiological studies show that NPS are common in AD. For example, 51% of new onset AD patients were observed to have had at least one NPS at baseline. The most common symptoms were depression (25%), apathy (17%), and irritability (17%) (Steinberg et al., 2014). Psychotropic medications, including antidepressants and antipsychotics, are widely used for the treatment of NPS in AD. Approximately one-third of AD patients take antidepressant or antipsychotic drugs (Gruber-Baldini et al., 2007; Kamble et al., 2009). Challenges in the design and interpretation of treatment studies of specific NPS have included a lack of consensus diagnosis, difficulties in measurement and the use of different assessment tools (Geda et al., 2013). These issues have been addressed to some extent by specific criteria proposed for psychosis and depression and by studies that have evaluated the sensitivity of different measures to detect change with treatment (Jeste and Finkel, 2000; Olin et al., 2002; Mayer et al., 2006). The use of psychotropic medications has been associated with harmful, as well as, potentially beneficial outcomes. For example, the use of psychotropic medications (including antidepressants, antipsychotics and benzodiazepines) was associated with more rapid cognitive and functional decline in AD over 3.7 years, and

not with improved NPS (Rosenberg et al., 2012). Moreover, several studies report an association between antipsychotic medication use and increased mortality (Wang et al., 2005; Simoni-Wastila et al., 2009). In terms of the treatment of psychosis, the CATIE-AD study observed that the atypical antipsychotics, such as olanzapine, quetiapine, risperidone were more effective for particular symptoms, such as anger, aggression, and paranoid ideation compared to placebo, but the medications did not improve functioning, care needs, or quality of life (Sultzer et al., 2008). The medications were associated with worsening cognitive function of a magnitude consistent with 1 year of dementia progression compared with placebo (Vigen et al., 2011). For the treatment of agitation, the mood stabilizer, valproate did not appear to be effective. Tariot et al report that valproate treatment did not delay emergence of agitation or slow cognitive or functional decline in moderate AD patients and was associated with significant toxic effects (Tariot et al., 2011). In another study, valproate was not effective for the management of agitation of moderate-to-severe AD patients (Herrmann et al., 2007).

In contrast, methylphenidate has been shown in several studies to be associated with decreased apathy and a trend toward improved global cognition (Rosenberg et al., 2013; Padala et al., 2010 and 2013; Lanctot et al., 2014). In terms of the treatment of depression, the single site “DIADS” study in AD patients who met DSM-IV criteria for major depression observed that selective serotonin reuptake inhibitors (SSRIs), sertraline was superior to placebo (Lyketsos et al., 2000). The follow-up, multi-site “DIADS-2” study in AD patients who met the Olin Criteria for depression in AD (a criteria that involves fewer and less frequent symptoms than the DSM-IV criteria for major depression: Olin et al., 2003) observed that sertraline treatment is not associated with improvement of depressive symptoms after 12 or 24 weeks of treatment (Rosenberg et al., 2010; Weintraub et al., 2010b). Preliminary studies of serotonin and norepinephrine reuptake inhibitors (SNRIs) in AD with depression reported the efficacy of milnacipran and mirtazapine (Mizukami et al., 2009; Raji and Brady, 2001). However, in a recent UK study comparing sertraline, mirtazapine and placebo in patients with probable or possible AD, there was no difference between either drug or placebo in patients treated for up to 39 weeks (Banerjee et al., 2011). Thus, while there is evidence that positive treatment effects have been found in studies using more (Lyketsos et al., 2000) versus less stringent depression criteria (Nyth and Gottfries, 1990), this observation has not been replicated recently (Drye et al., 2011; Banerjee et al., 2011). Thus, clinical trials of SSRI and SNRI antidepressants across a range of depression severities and treatment durations have not shown that these classes of antidepressants significantly reduce depressive symptoms to a greater extent than placebo. While the negative findings could be due to issues in study design and measurement, these observations suggest that other neurochemical or molecular mechanisms should be considered, as well as brain stimulation (TMS) and behavior therapy (psychotherapy, cognitive therapy). Thus, many treatment studies of NPS using medications that are effective in treating such symptoms in younger patients do not show a significant benefit in treating such symptoms in AD. These studies underscore the importance of using molecular imaging methods to understand the specific neurochemical and neuropathological mechanisms associated with NPS in AD.

2.2 Cerebral Glucose Metabolism and Blood Flow

In AD, deficits in regional cerebral blood flow (rCBF) and glucose metabolism have been reported most consistently in temporo-parietal cortical association areas, with relative sparing of primary sensory (visual, somatosensory) and motor cortical areas, basal ganglia, thalamus and cerebellum (Ferris et al., 1983; Friedland et al., 1983; McGeer et al., 1990; Kumar et al., 1991; Smith et al., 1992; Matsuda, 2001). Both between and within subjects, the regional pattern of deficits initially observed (i.e. vulnerability of heteromodal association cortices) is accentuated (Smith et al., 1992; Sanabria-Diaz et al., 2013). Studies of cerebral metabolism and rCBF can distinguish among the degenerative dementias (e.g. multi-infarct dementia, Pick's disease, normal pressure hydrocephalus) and the severity of the deficits in cerebral metabolism and rCBF is correlated with global disease severity and neuropsychological function (Jagust et al., 1985). The available data has demonstrated a high degree of correspondence between regional deficits in cerebral glucose metabolism and the regional distribution of neuropathologic markers observed at post-mortem examination (McGeer et al., 1986). Having identified the brain regions affected in AD using measurements of rCBF and glucose metabolism, mechanistic hypotheses based upon the known regional distribution of neurotransmitter receptors and terminal projections and neuropathology can be generated and tested using PET radiotracers.

Several studies have evaluated changes in cerebral metabolism and rCBF associated with NPS in AD patients. Significant correlations were observed between greater agitation/disinhibition factor scores and frontal and temporal cortical hypometabolism, between higher psychosis factor scores and frontal cortical hypometabolism, and between higher anxiety/depression factor scores and parietal cortical hypometabolism (Sultzer et al., 1995). Further, delusions in AD were associated with hypometabolism in the right superior dorsolateral frontal cortex, the right inferior frontal cortex, the right lateral orbitofrontal cortex and bilateral temporal cortex (Sultzer et al., 2003; Sultzer et al., 2013). A rCBF study reported that AD patients with psychotic symptoms had significantly lower rCBF in the left dorsolateral frontal and medial temporal cortices than AD patients without psychotic symptoms (Lopez et al., 2001). Depressive symptoms in AD were associated with decreased rCBF in the anterior cingulate and superior temporal, bilaterally, left dorsolateral prefrontal, right middle temporal, and right parietal cortices. Further, a review of the literature concluded that decreases in prefrontal areas, including dorsolateral prefrontal cortex, orbitofrontal cortex, or anterior cingulate cortex have been implicated in both primary and secondary depression in many studies (Rogers et al., 1998). Emotional lability was associated with decreased rCBF in the anterior cingulate and dorsolateral prefrontal cortices bilaterally, and in the left basal ganglia. Apathy was also associated with decreased rCBF in the basal ganglia and the dorsolateral prefrontal cortex, bilaterally (Lopez et al., 2001). Similarly, apathy in AD was associated with reduced metabolic activity in the bilateral anterior cingulate gyrus, medial orbitofrontal cortex and medial thalamus, which were independent of depressive symptoms (Marshall et al., 2007). Higher anxiety in AD was associated with lower metabolism in temporo-limbic structures, including the bilateral entorhinal cortex, anterior parahippocampal gyrus, left anterior superior temporal gyrus and insula (Hashimoto et al., 2006). In summary, depression, emotional lability and apathy in AD are associated with greater cortical-subcortical dysfunction than in AD without these

symptoms in overlapping frontal and temporal cortical regions. Greater reductions in rCBF and metabolism are associated with NPS in AD patients with compared to AD patients without NPS.

3. Molecular Imaging in Alzheimer's disease

3.1 Dopamine System

Post-mortem studies observed that the loss of cholinergic, noradrenergic and serotonergic innervation to the cortex occurs at an early stage in AD, while dopaminergic innervation remains relatively intact, especially the nigro-striatal dopamine system (as reviewed by Palmer, 1996). In contrast, the mesolimbic-dopamine system is selectively affected in AD (Trillo et al., 2013). Neuroimaging studies have shown relative sparing of striatal dopamine metabolism or dopamine transporters in AD compared with healthy controls, but decreases in patients with dementia with Lewy bodies (DLB). In fact, good differential diagnosis of AD from DLB is consistently observed using neuroimaging measures of the striatal dopamine transporter (Itoh et al., 1994; Walker et al., 2002).

Several studies have reported that dysfunction within cortico-striatal dopaminergic neural circuits is associated with NPS in AD. Many of the studies to examine the role of the striatal dopamine (D2/D3) receptors have employed the radiotracer [11C]-raclopride. It is important to note that [^{11}C]-raclopride has a comparable affinity as dopamine for binding to the D2/3 receptor. Thus, higher dopamine concentrations would be associated with lower D2/3 receptor availability and lower dopamine concentrations would be associated with higher D2/3 receptor availability. Reeves et al reported that striatal dopamine (D2/D3) receptors are increased in AD patients with compared to AD patients without delusions (Reeves et al., 2009). In contrast, lower striatal dopamine D2 receptors was associated with greater impairments in motor speed, attentional performance and episodic memory. Higher striatal D2 receptors were associated with wandering behavior (Meguro et al., 1997). Lower striatal D2 receptors in AD patients was associated with greater behavioral disturbance (higher behavioral pathology in Alzheimer's disease frequency weighted severity scale [BEHAVE-AD-FW scores] (Tanaka et al., 2003). Further, lower striatal DA transporter availability ([^{123}I]-FP-CIT) was correlated with greater apathy in a combined AD and DLB sample (David et al., 2008). Based on the available data, greater overall behavioral disturbance is associated with lower striatal D2 receptors, higher striatal D2 receptors is associated with delusions and wandering behavior and lower dopamine transporters are associated with apathy. As mentioned above, given that the D2 radiotracer used in these studies, [^{11}C]-raclopride, competes with dopamine for binding to the receptor, these findings may be associated with higher and lower striatal dopamine concentrations, respectively. This may explain the discrepancy between the lack of change of the dopamine system in post-mortem studies and the in vivo changes in striatal D2 receptors associated with NPS. Further, one hypothesis that has been suggested is that in AD progressive cholinergic loss (resulting in a loss of inhibition of the dopamine system), in the context of a relatively spared dopaminergic system, may increase the tendency of AD patients to develop psychosis because of a relative striatal hyperdopaminergia (Cummings and Back, 1998).

3.2 Serotonin System

With respect to neurochemical imaging in AD, the majority of studies have focused on the serotonin system. In fact, several studies have demonstrated that the serotonergic deficits (cell body loss, levels and metabolites) in AD are greater and more widespread than other monoaminergic (dopamine, norepinephrine) deficits in AD (Zweig et al., 1988; Baker and Reynolds, 1989; Nazarali and Reynolds, 1992; Palmer et al., 1987). Post-mortem studies in AD consistently observed reduced serotonin levels, receptors (5-HT2A), reuptake sites and metabolites (5-HIAA) in frontal and temporal cortical areas, (Palmer et al., 1988; D'Amato et al., 1987a; Bowen et al., 1983; Cross et al., 1983; Volicer et al., 1985; Sparks, 1989; Bowen et al., 1979) as well as the correlation with NPS and cognitive decline. Lower temporal cortical 5-HT1b/d and 5-HT2A receptors correlated with rates of cognitive decline in AD, and in the case of the 5-HT2A receptor the correlation was independent of choline acetyltransferase concentrations (Lai et al., 2005). Lower 5-HT1A receptors were correlated with greater depressive symptoms and lower 5-HT6 receptors with overactivity and aggression (Lai et al., 2011). Lower 5-HT concentrations in temporal cortex were associated with hyperactivity and psychosis (Garcia-Alloza et al., 2005).

Molecular imaging studies of the serotonin system show results that are consistent with post-mortem studies in demonstrating a substantial reduction of serotonin transporter and receptors in AD. Several studies have shown correlations between greater serotonin deficits and NPS. Reduced serotonin transporters, ([^{11}C]-DASB) were observed in mesial temporal cortex in AD (Marner et al., 2012). In contrast, serotonin transporters ([^{11}C]-DASB) in the putamen were significantly lower in AD, regardless of depression, than healthy controls. The depressed AD group showed greater and more extensive reductions in serotonin transporters that included the midbrain, nucleus accumbens and thalamus (Ouchi et al., 2009). Further, correlational analyses showed that glucose metabolism in the right dorsolateral prefrontal cortex (DLPFC) was positively correlated with the level of striatal serotonin transporters ([^{11}C]-DASB) in AD, suggesting that the subcortical serotonergic dysfunction may affect the cortical function in regions implicated in affective processing such as the DLPFC.

With respect to the 5-HT1A receptor, a significant decrease of 5-HT1A receptors ([^{11}C]WAY-100635) was reported in medial temporal cortex in AD (Lanctot et al., 2007). Further, a significant reduction of 5-HT1A receptors in hippocampus in AD compared to normal controls has been reported (Kepe et al., 2006). A global decrease in cortical 5-HT1A receptors, ([^{18}F]MPPF) was observed in AD in contrast to a global increase in amnestic mild cognitive impairment (MCI) compared to controls. In amnestic MCI, hippocampal 5-HT1A receptors were 59 % higher than the controls, and conversely, 35 % lower in mild AD relative to controls (Truchot et al., 2008; Truchot et al., 2007). These results may suggest a compensatory up-regulation of the 5-H1A receptor in amnestic MCI stage prior the observed reduction in AD that might be associated with greater cortical pathology. The reduction of hippocampal 5-HT1A receptors correlated with greater cognitive impairment (MMSE), greater reduction of glucose metabolism in posterior cingulate cortex and medial temporal lobe and greater AD neuropathology ([^{18}F]-FDDNP) in a combined group of normals, MCI and AD (Kepe et al., 2006). The increase of 5-HT1A receptors and the functional

significance in MCI is controversial and should be explored in further studies with respect to cognitive deficits and NPS.

5-HT2A receptor imaging studies ([^{18}F]setoperone) have demonstrated a global decrease of cortical receptors in AD (Blin et al., 1993). One study of the 5-HT2A receptor ([^{18}F]deuteroaltanserin) observed a selective reduction of 5-HT2A in the anterior cingulate and no significant correlations between regional 5-HT2A receptors and behavioral measures (CSDD, BPRS, NPI and Psychosis Score), including depressive and psychotic symptoms (Santhosh et al., 2009). Furthermore, in patients with MCI, a 20–30% reduction in cortical 5HT2A receptors is observed compared to controls. Longitudinal studies show that the reduction in cortical 5-HT2A receptor is relatively stable over time, even in MCI patients who convert to AD (Marner et al., 2011). Reduced 5-HT2A receptors in the striatum correlated significantly with greater Neuropsychiatric Inventory depression and anxiety scores in MCI (Hasselbalch et al., 2008). Thus, the limited available data suggest that the decrease in cortical 5-HT2A receptors is correlated with NPS in MCI, but not AD.

3.3 Cholinergic System

The cholinergic deficit in AD was reported over 30 years ago. Neuronal loss in the cell bodies of the cortical cholinergic projections (nucleus Basalis of Meynert, nBM), as well as the loss of choline acetyltransferase (ChAT) in cortical areas has been observed in AD (Davies and Maloney, 1976; Perry et al., 1978; Whitehouse et al., 1981; Whitehouse et al., 1982). Studies over the past decade have shown that the cortical and hippocampal cholinergic deficits occur later in the course of AD (Davis et al., 1999). Both no change and an up-regulation of ChAT have been reported in MCI (Davis et al., 1999). However, decreased trophic responses in nBM neurons are observed in MCI and early AD (Mufson et al., 2007). Nonetheless, among the neurochemical abnormalities reported in AD, the cholinergic deficit is the strongest neurochemical correlate of dementia severity (Blessed et al., 1968; Bierer et al., 1995; DeKosky and Scheff, 1990; DeKosky et al., 1992). With respect to cholinergic receptor alterations, a modest loss of muscarinic receptors is observed in AD, mainly the M2 subtype (Mash et al., 1985). The loss of cortical nicotinic cholinergic receptors has been reported more consistently (Flynn and Mash, 1986; Whitehouse et al., 1988; London et al., 1989). The magnitude of decrease in nicotinic cholinergic receptors is greater than muscarinic receptors (Whitehouse and Au, 1986). With respect to the specific nicotinic cholinergic receptor subtype affected in AD, several studies have demonstrated that the alpha4-beta2 ($\alpha4\beta2$) nicotinic acetylcholine receptor is most affected in temporal cortex, hippocampus and striatum (Burghaus et al., 2000; Court et al., 2000). A greater decrease in $\alpha4$ nicotinic acetylcholine receptor immunoreactivity was observed in temporal cortex and striatum, in the absence of change in $\alpha7$ nicotinic acetylcholine receptor, consistent with some other studies (Gotti et al., 2006; Martin-Ruiz et al., 1999; Guan et al., 2000). In contrast, a loss of $\alpha4\beta2$ nicotinic acetylcholine receptors in layer 3 of entorhinal cortex and $\alpha7$ nicotinic acetylcholine receptor in layer 2 of the subiculum in AD has been reported (Teaktong et al., 2004). $\alpha7$ nicotinic acetylcholine receptor immunoreactivity was increased in astrocytes in the hippocampus and entorhinal. Studies of the $\alpha7$ nicotinic acetylcholine receptor in basal forebrain show an increase in AD compared to controls and no difference in MCI relative to controls (Counts et al., 2007).

While the cholinergic deficit has been a focus of post-mortem studies for many years, *in vivo* studies have been limited by challenges in radiotracer development and quantification. Studies of acetylcholinesterase and vesicular acetylcholine transporter concentrations show reductions in AD patients, but the reduction are greater in PD patients, especially those with dementia (Kuhl et al., 1999; Kuhl et al., 1996; Bohnen et al., 2003). Studies of the muscarinic receptor have shown either reductions in cortical regions or no change in AD relative to controls (Zubieta et al., 2001; Weinberger et al., 1992).

The initial PET studies of the nicotinic receptor in AD, using [^{11}C] nicotine (that binds to high affinity sites including α4β2), showed a decrease in temporal, parietal and occipital cortices and putamen (Nordberg, 1994). A recent study showed that frontal and parietal receptors were correlated with tests of attention, rather than episodic memory, consistent with the role of nicotine in cognition (Kadir et al., 2006). Subsequent studies have been performed with SPECT and PET radiotracers for alpha4-beta2 nicotinic acetylcholine (α4β2-nACh) receptors. SPECT studies using [^{123}I]-5-IA-85380 showed decreased receptors in the medial temporal cortex in amnesic MCI subjects and decreased receptors in frontal and striatal regions (bilaterally) and right medial temporal cortex in moderately impaired AD patients (Terriere et al., 2008; O'Brien et al., 2007). In a PET study using the radiotracer 2-[^{18}F]-fluoro-A-85380, Ellis et al observed a non-significant increase in α4β2 nicotinic acetylcholine receptors in early AD patients relative to controls (Ellis et al., 2009). In contrast, Sabri et al reported decreased α4β2 nicotinic acetylcholine receptors were in both MCI and AD patients in cortical, striatal and hippocampal regions using the same radiotracer (Kendziorra et al., 2011). The differences in results between studies could be related to differences in radiotracer quantification methods or patient characteristics. In vascular dementia, decreased α4β2 nicotinic acetylcholine receptors were observed in sub-cortical regions including the thalamus (bilaterally) and right caudate in contrast to the loss of cortical α4β2 nicotinic acetylcholine receptor were reported in AD (Colloby et al., 2011). Thus far, the significance of nicotinic receptor loss in MCI and AD with respect to NPS has not been the focus of investigation.

3.4. Neuropathology

The development of radiotracers to image beta-amyloid deposition, one of the pathological hallmarks of AD (in addition to hyperphosphorylated tau), is a significant advance in AD neuroimaging. PET radiotracers for beta-amyloid deposition show good diagnostic sensitivity between normal elderly, MCI and AD ([^{18}F]-FDDNP, [^{11}C]-SB13, [^{11}C]-PiB; Shoghi-Jadid et al., 2002; Small et al., 2006; Verhoeff et al., 2004; Klunk et al., 2004; Rowe et al., 2007; Pike et al., 2007; Forsberg et al., 2008). [^{11}C]-PiB is the best characterized and most commonly used radiotracer and has high affinity and specificity for amyloid in AD brain (Mathis et al., 2003; Ikonomovic et al., 2008). In AD, the regional distribution of [^{11}C]-PiB is similar to post-mortem studies of beta-amyloid deposition, including frontal, temporal, and parietal cortices (Ziolko et al., 2006; Arnold et al., 1991). 52–87% of MCI subjects show elevated [^{11}C]-PiB across studies (Rabinovici and Jagust, 2009). Combined measures of beta-amyloid deposition and glucose metabolism provide better diagnostic accuracy for MCI than either measure alone,(e.g. Li et al., 2008) which suggests that the functional consequences of beta-amyloid deposition should be considered. The correlation

between [^{11}C]-PiB and cognitive impairment in normal controls, MCI and AD is controversial (Sojkova et al., 2008; Aizenstein et al., 2008). Some studies show that the association between beta-amyloid deposition and memory impairment in controls is mediated by hippocampal volume reductions (Mormino et al., 2009; Jack et al., 2009). However, higher cortical [^{11}C]-PiB in both normal controls and MCI subjects is associated with cognitive decline (Resnick et al., 2010; Villemagne et al., 2008; Pike et al., 2007; Forsberg et al., 2008; Kemppainen et al., 2007; Morris et al., 2009). Higher baseline beta-amyloid deposition may precede cognitive impairment and predict cognitive decline. There is some evidence for an association between beta-amyloid deposition and NPS (especially depression and apathy). Increased beta-amyloid deposition is observed in depressed MCI subjects, non-depressed MCI subjects and depressive and anxiety symptoms are associated with higher [^{18}F]-FDDNP binding in normal controls (Butters et al., 2008; Lavretsky et al., 2009). In terms of apathy, the apathy subscale of the neuropsychiatry inventory (NPI) was correlated with greater [^{11}C]-PiB retention in the bilateral frontal and the right anterior cingulate and that [^{11}C]-PiB retention was greater in the bilateral frontal cortex of AD with than those of without apathy (Mori et al., 2014).

A recent focus in radiotracer chemistry is the development of peripheral benzodiazepine receptor (PBR) radiotracers that bind with high affinity to translocator protein (TSPO). TSPO is up-regulated in activated microglia and represents a marker of neuroinflammation. Post-mortem studies have revealed age-related increases in microglia (Brown, 2009; Sheng et al., 1998). Several studies have shown increased cortical TSPO binding in AD, but not MCI (Kreisl et al., 2013; Schuitemaker et al., 2013). Some studies have not shown increased cortical TSPO binding in AD ([^{11}C]-PK11195; Wiley et al., 2009). In AD, greater TSPO binding ([^{11}C]-PBR28) was correlated with worse performance on the MMSE, Clinical Dementia Rating Scale (CDR) Sum of Boxes, Logical Memory immediate (Wechsler Memory Scale Third Edition), Trail making part B and Block Design (Wechsler Adult Intelligence Scale Third Edition), to the greatest extent in inferior parietal lobule (Kreisl et al., 2013). Overlap between cortical TSPO binding ([^{11}C](R)PK11195) and beta-amyloid deposition ([^{11}C]-PiB) in AD has been observed (Edison et al., 2008). Thus, these studies suggest that inflammation is detected after the conversion of MCI to AD and that there may be some relationships between microglial activation and beta-amyloid deposition in AD. Given the potential role of inflammation in neuropsychiatric symptoms, especially mood symptoms (Haroon et al., 2012), future work should evaluate NPS relative to inflammation in AD and MCI.

4. Parkinson’s Disease (PD)

PD is a neurodegenerative disease that presents with resting tremors, bradykinesia, postural instability, and rigidity and is associated with the loss of dopamine in the nigro-striatal dopamine system (Fearnley and Lees, 1991). Non-motor symptoms, such as anxiety and depression are also common (Chaudhuri et al., 2006) and can have a great impact on patient’s quality of life. Cognitive deficits in such domains as mental status (modified mini mental status test), verbal episodic, olfactory and visuo-spatial memory and executive function have been observed, as reviewed (Bohnen et al., 2010). Recent neuroimaging studies have been conducted to investigate the neurobiology of NPS in PD.

4.1 The treatment of NPS in Parkinson's disease

The treatment of NPS in PD is complicated by overlap with motor and non-motor symptoms of PD, anti-parkinsonian medication side effects, frequent comorbidity with other NPS, and an increased vulnerability to the side effects of certain psychotropic drugs (Aarsland et al., 2009). While NPS are present across all stages of PD, they become increasingly problematic as the disease progresses and are major determinants of disability, quality of life, and nursing home placement in advanced stages of the disease (Hely et al., 2005).

Depression is one of the most common NPS in PD, occurring in up to 50% of patients (Reijnders et al., 2008). Despite a number of open label and controlled trials, a recent evidence based review by members of the Movement Disorder Society determined that repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), SSRIs, SNRIs, Monoamine Oxidase Inhibitors (MAOIs), and newer antidepressants like atomoxetine and nefazodone have insufficient evidence for efficacy for the treatment of depression in PD (Seppi et al., 2011). Among "traditional" antidepressant drug classes, only the tricyclic drugs, nortriptyline and desipramine have been evaluated as "likely efficacious" with randomized controlled trials (RCTs) demonstrating superiority to placebo (Menza et al., 2009; Devos et al., 2008). In addition, SSRIs and SNRIs, which are typically well tolerated in the general population, may worsen tremor and other motor symptoms in PD (Frisina et al., 2008; Kulisevsky et al., 2008) and tricyclics can increase the risk of falls and contribute to an increased risk of delirium and confusion (Bloem et al., 2001; Frisina et al., 2008). Several studies suggest dopamine deficiency, more than serotonin or norepinephrine dysregulation, plays a role in PD depression as depressive episodes often coincide with "off-periods", when dopaminergic drugs wear off at the end of dose or fluctuate over the treatment interval (Maricle et al., 1995; Witjas et al., 2002). Consistent with these observations, Baron et al conducted two randomized controlled trials of the dopamine agonist pramipexole. Both studies found that pramipexole is efficacious for the treatment of depression in PD (Barone et al., 2006; Barone et al., 2010). However there is an association between pramipexole and other dopamine agonists and a 2–3.5 fold increased odds of another NPS, impulse control disorders (ICDs) (Weintraub et al., 2010a). ICDs are behavioral disorders that typically manifest as pathological gambling, hypersexuality, and compulsive spending, shopping, or eating. These ICDs individually or in various combinations were identified in 17.1% of patients treated with dopamine agonists compared to 6.9% of patients not on dopamine agonists in a study of over 3000 PD patients. Currently, there are two RCTs to treat ICDs in PD, one was a 17-week trial of amantadine for pathological gambling and the other tested naltrexone for all ICDs. Although the amantadine arm of the trial showed a statistically significant reduction on the Gambling-Symptom Assessment Scale and the Yale-Brown Obsessive-Compulsive Scale compared to the placebo arm, it is deemed to be preliminary due to a small sample size (n=17), lack of replication, and no more than 4 weeks on drug (Thomas et al., 2010). Similarly, subjects on naltrexone compared to placebo showed greater improvement on a self-rated PD-specific ICD scale, but did not show improvement on a clinician rated global assessment of ICD remission (Weintraub et al., 2010a).

Clinically significant anxiety occurs in up to 40% of patients with PD and often co-occurs with depression (Pontone et al., 2009; Leentjens et al., 2011). Similar to depression, anxiety has been associated with worse quality of life, greater motor impairment, more dyskinesias, and a greater frequency of motor fluctuations (Witjas et al., 2002; Carod-Artal et al., 2008; Siemers et al., 1993; Pontone et al., 2009; Dissanayaka et al., 2010). Association with the movement symptoms of PD suggests that, in many cases, there may be an interdependent treatment response between motor and anxiety symptoms requiring treatment outside of the usual regimen for anxiety in the general population. In addition, many conventional anxiety treatments, like benzodiazepines and antidepressants, can be problematic when used in PD, increasing confusion and the risk of falls (Bloem et al., 2001; Frisina et al., 2008; Kulisevsky et al., 2008). Despite the distress and dysfunction caused by anxiety syndromes and their unusually high prevalence in PD there are no RCTs on which to establish evidence-based treatment (Seppi et al., 2011).

Finally, psychosis in PD presents a significant treatment paradox as the dopamine needed to improve motor function has been implicated in increasing the frequency and severity of hallucinations and delusions and the medications most often used to treat these psychotic symptoms block dopamine and cause parkinsonism (Fenelon and Alves, 2010). All typical and most atypical antipsychotics are contraindicated in PD because they worsen motor function and carry a higher risk for adverse events including cognitive decline, confusion, drowsiness, and in some cases an increased risk of mortality (Marras et al., 2012). Quetiapine and clozapine are exceptions in that they do not appear to appreciably worsen motor function. However, only clozapine has been adequately tested to demonstrate improvement in hallucinations without worsening motor function (Factor et al., 2001; Morgante et al., 2004). However, clozapine carries significant risks including, life threatening agranulocytosis, which requires continuous blood monitoring, orthostatic hypotension, confusion, and somnolence.

The limited evidence for efficacy with standard psychotropic medications, the overlap between NPS and PD symptoms, and the increased vulnerability to side effects suggests the need for molecular imaging studies to help better understand the neurophysiologic underpinnings of NPS and potential treatments in PD.

4.2 Cerebral Glucose Metabolism and Blood Flow

PET studies in early stages of PD have reported relatively increased oxygen and glucose metabolism in the external pallidum, internal pallidum, thalamic subnuclei, and the putamen which is likely to be caused by increased external pallidal activity (Borghammer et al., 2012). Several studies have investigated neural networks of motor and non-motor symptoms in PD. Eidelberg et al identified a motor network in which higher metabolic activity in the lentiform nucleus and thalamus was associated with lower activity in the lateral frontal, paracentral, inferior parietal, and parieto-occipital areas and increased metabolism in the lentiform nucleus and thalamus (Eidelberg et al., 1994). Decreased expression of this network was associated with motor symptom improvement across interventions including pharmacotherapy (levo-dopa) and deep brain stimulation (Hirano et al., 2009). Greater brain activation in a motor sequence learning task in the left DLPFC, pre-supplementary motor

area, and bilaterally in the superior parietal cortex was observed in the presence of a normal level of performance, which may suggest that increased activation of cortico-cortical pathways can compensate for striatal-cortical dysfunction (Fukuda et al., 2001).

In addition to the motor networks identified, networks associated with cognitive impairment have been identified. In non-demented PD patients, a covariance pattern associated with verbal memory (California Verbal Learning Test) and executive functioning (Stroop test) was identified that consisted of reduced metabolism in cortical areas including the pre-supplementary motor area (pre-SMA) and precuneus, the dorsal premotor cortex, and the inferior parietal lobule and relative increases in the cerebellar vermis and dentate. Unlike the motor network, changes in expression of the cognitive network were not observed with levodopa or deep brain stimulation (DBS) treatments (Huang et al., 2007). Increased expression of this cognitive network was associated with lower caudate dopamine transporters ([^{18}F]-fluoropropyl-ß-CIT; Niethammer et al., 2013). Decreased expression of the cognitive network in PD with MCI than in PD without MCI was reported (Huang et al., 2008). Further, two independent glucose metabolism networks were associated with cognitive impairment and depressive symptoms in non-demented PD patients using brain-behavior partial least squares. The network associated with visuo-spatial (Hooper Visual Organization Test) and memory functioning (California Verbal Learning) included parieto-occipito-temporal and medial temporal brain regions and the network associated with depressive symptoms included lateral/medial frontal cortex, orbitofrontal cortex, and anterior cingulate cortex (Mentis et al., 2002). Other studies of depression in PD and shown lower frontal cortical metabolism and blood flow. Mayberg et al reported that metabolic activity in the caudate and orbital-inferior frontal cortex was significantly lower in depressed as compared to non-depressed PD and control subjects and that there was a significant inverse correlation between lower glucose metabolism in those areas and greater depression scores (Mayberg et al., 1990). Similarly, hypoperfusion of the medial frontal cortex and the anterior cingulate cortex in PD with compared to PD without depression was observed (Ring et al., 1994). Matsui et al also observed hypoperfusion of the left superior and inferior frontal cortex in depressed compared to non-depressed PD (Matsui et al., 2006). Thus, lower frontal glucose metabolism is consistently associated with depression in PD.

5. Molecular Imaging in Parkinson's disease

5.1 Dopamine system

As mentioned, PD involves progressive degeneration of the nigro-striatal dopamine system (Fearnley and Lees, 1991; Hughes et al., 1992). The pathology of the nigro-striatal dopamine system is visualized in in vivo by molecular imaging studies that consistently report reductions of the striatal dopamine transporter, dopamine metabolism and the vesicular monoamine transporter (VMAT2) in PD compared to controls (Walker et al., 2004; Guttman et al., 1997; Brooks et al., 1990; Brooks, 2010; Holthoff-Detto et al., 1997; Frey et al., 1996; Goto et al., 1989; Rinne et al., 1989). These neuroimaging targets have been evaluated as diagnostic and prognostic biomarkers of PD (Parnetti et al., 2013; Schapira, 2013). Postmortem studies of three dopamine receptor subtypes (D1, D2 and D3), observed the most striking changes were the elevation of D2 receptors in the rostral putamen

(71%), elevation of D1 receptors in the caudal striatum (30%), and decrease in D3 receptors in the caudal striatum (13%) in PD compared to elderly controls (Piggott et al., 1999). Molecular imaging studies have shown that putamen D2 receptors range from normal to moderately up-regulated and caudate D2 receptors do not differ significantly compared to controls (as reviewed by Brooks et al., 2010).

Regarding the relationship between the dopamine transporters and depressive symptoms in PD, a greater loss of dopamine/norepinephrine transporters ([^{11}C]-RTI-32) was observed in the locus coeruleus and in the several regions of the limbic system including anterior cingulate cortex, thalamus, amygdala and ventral striatum in depressed PD compared to non-depressed PD patients (Remy et al., 2005). In contrast, higher striatal dopamine transporter density is observed in PD with depression was observed in a SPECT study using [^{99m}Tc]-TRODAT-1) (Felicio et al., 2010). However, using the same radiotracer in a large sample of patients (n=76), Weintraub and colleagues (Weintraub et al., 2004), observed that lower left putamen dopamine transporter binding was associated with greater depression and anxiety symptoms in patients with less severe PD. Higher depression scores were associated with lower striatal dopamine metabolism (6-[^{18}F]fluorodopa; Joutsa et al., 2013). With respect to anxiety symptoms, in never-treated PD patients with compared to those without anxiety, striatal dopamine transporters (SPECT with [^{123}I]-FP-CIT) were significantly lower. While the dopaminergic deficits is worse in PD patients with depression compared to those without in the majority of studies, stage of illness should be considered in the interpretation of the data. Greater anxiety severity was associated with decreased dopamine transporter availability in right caudate in the combined PD group (Erro et al., 2012). The observation of treatment (dopamine agonist and DBS) induced impulse control disorders had led to molecular imaging studies to investigate the underlying neurochemical mechanisms. Increased ventral striatum dopamine release ([^{11}C]-raclopride) measured during a gambling task was observed in PD patients with compared to those without pathological gambling (Steeves et al., 2009). A follow-up study of extra-striatal D2 receptors ([^{11}C] FLB-457) showed that midbrain dopamine release during a gambling task was blunted in PD patients with compared to those without pathological gambling. However, PD patients with had significantly greater D2 receptors in the anterior cingulate gyrus compared to those without pathological gambling (Ray et al., 2012). Thus, the majority of studies show that depressive and anxiety symptoms, as well as pathological gambling, are associated with greater striatal dopamine dysfunction.

Several studies have shown an association between dopamine metabolism and motor function, as well as cognition in PD. Non-demented, un-medicated, early stage PD patients have decreased striatal and increased cortical (parieto-frontal areas including precuneus and cingulate gyrus, right middle frontal gyrus, and bilateral medial frontal and cingulate gyrus) dopamine metabolism (6-[^{18}F]fluorodopa) compared to controls. Reaction time, in a test measuring sustained attention, correlated positively with dopamine metabolism in dorsolateral prefrontal cortex. Poorer performance in the Stroop test correlated with greater dopamine metabolism in the medial frontal cortex and the anterior cingulate which may suggest that the changes in frontal dopamine metabolism are related to cognitive impairments found in early PD (Bruck et al., 2005).

5.2 Serotonin System

With respect to monoamine systems, noradrenaline and serotonin, as well as dopamine, may significantly contribute to NPS as these systems have been shown to degenerate in PD, in addition to the dopamine system (Dauer and Przedborski, 2003; Fahn and Sulzer, 2004; Rommelfanger and Weinshenker, 2007; D'Amato et al., 1987b; Kish et al., 2008). The serotonin system has been evaluated in imaging studies of PD. Significant decreases in serotonin transporters ([^{11}C]-DASB) in striatal, brainstem, and cortical regions were observed in PD compared to controls, that was not significantly correlated with PD stage, motor symptoms, disease duration or degree of exposure to dopaminergic therapy, which may suggest that serotonergic dysfunction may not be associated with motor symptoms (Politis et al., 2010a). In contrast, reductions in 5-HT1A receptors have been reported in the raphe and were correlated with tremor in this study (Doder et al., 2003). Studies have shown that the serotonin system is implicated in NPS in PD. In depressed, early stage PD patients, the serotonin transporter ([^{11}C]-DASB) was significantly increased in dorsolateral (37%) and prefrontal (68%) cortices compared to controls. Greater serotonin transporters were correlated with greater depressive symptoms (Boileau et al., 2008). Increased serotonin transporters ([^{11}C]-DASB) in depressed PD patients was observed in a second study in the amygdala, hypothalamus, caudal raphe nuclei, and posterior cingulate cortex, in contrast to reduced serotonin transporters in PD compared to controls (Politis et al., 2010b). Depressive symptoms in PD correlate with higher serotonin transporters ([^{11}C]-DASB) in raphe and limbic systems (Politis et al., 2010b). PD patients with depression showed reduced 5-HT1A receptors ([^{18}F]-MPPF) in the left hippocampus, the right insula, the left superior temporal cortex, and the orbitofrontal cortex compared to PD without depression (Ballanger et al., 2012). PD patients with visual hallucinations demonstrated increased 5-HT2A receptors in the ventral visual pathway (including the bilateral inferooccipital gyrus, right fusiform gyrus, and inferotemporal cortex), as well as the bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula (Ballanger et al., 2010). These studies implicate the serotonin system in several aspects of NPS, including depression and visual hallucinations, in PD. The nature of serotonin dysfunction and the relationship to other neurotransmitter changes is an important area of further investigation.

5.3 Cholinergic System

With respect to the cholinergic system, the basal forebrain (nucleus basalis of Meynert) and brainstem (pedunculo-pontine) cholinergic neurons are significantly reduced in PD compared to elderly controls in post-mortem studies (Nakano and Hirano, 1984: Zweig et al., 1989). Neuroimaging studies have shown significant decreases in acetycholinesterase concentrations in PD relative to controls ([^{11}C]methyl-4-piperidinyl propionate) (Kotagal et al., 2013). In fact, the neocortical cholinergic deficits in parkinsonian dementia is greater than in AD (Bohnen and Frey, 2007). PD patients with the greatest decreases in neocortical acetylcholinesterase activity had significantly lower cognitive performance (verbal learning, executive function, and attention domains) compared with the PD patients within the normal range, even after co-varying for the degree of nigrostriatal degeneration with striatal VMAT2 imaging ([^{11}C]-dihydrotetrabenazine; Bohnen et al., 2012).

5.4. Neuropathology

Several recent beta-amyloid imaging studies have shown that in PD, beta-amyloid deposition ([^{11}C]-PiB) is correlated with cognitive impairment. Higher global cortical beta-amyloid deposition was related to greater deficits in executive function and visuospatial function in PD (Gomperts et al., 2013). Global mean cortical beta-amyloid ([^{11}C]-PiB) was related to a poorer global cognitive function (composite of memory, visuo-spatial processing, working memory/attention, and executive function), as well as lower Wechsler Adult Intelligence Scale score (WAIS) in PD (Petrou et al., 2012). Another study demonstrated increased beta-amyloid deposition ([^{11}C]-PiB) only in the pons and mesencephalon in PD with cognitive impairment in the absence of cortical beta-amyloid deposition which suggested that the regional distribution of beta-amyloid deposition ([^{11}C]-PiB) and the relationship to cognitive deficits may be different between PD and AD (Campbell et al., 2013). Beta-amyloid deposition was associated with decreased serotonin transporters in PD in cortical and striatal regions (Kotagal et al., 2012). Several studies have shown evidence of inflammation (increased binding of the radiotracer ([^{11}C](R)-PK11195 to activated microglia) in PD (Gerhard et al., 2006; Ouchi et al., 2005), as reviewed by Politis et al (Politis et al., 2012). Increased radiotracer binding was observed in in cortical (pre-central gyrus, frontal lobe and anterior and posterior cingulate gyrus) and subcortical (striatum, pallidum, thalamus, midbrain and pons) regions. Increased midbrain binding was correlated with lower dopamine transporter binding and greater severity of motor symptoms (Gerhard et al., 2006; Ouchi et al., 2005). However, longitudinal increases in binding are not observed despite disease progression (Gerhard et al., 2006). Thus, beta-amyloid deposition and associated serotonin degeneration and neuroinflammation are observed in PD. The relationships between these aspects of pathology, which are also observed in AD and the association with motor, cognitive and NPS remains to be elucidated.

6. Conclusion

Molecular imaging studies in AD and PD have observed changes in neural circuitry and in specific neurochemical and neuropathological mechanisms, largely consistent with the postmortem literature, in the respective conditions. The available molecular imaging studies of NPS in these conditions have generally demonstrated a greater involvement of the neural circuitry affected a greater degree of pathology than observed in the absence of NPS or evidence of a reactive or a potential compensatory process (e.g. increased cortical serotonin transporters in depression in PD). NPS are common in AD and PD and have a substantial impact on the course and clinical management (including institutionalization) of neurodegenerative disease (Steinberg et al., 2008; Rabins PV et al., 2006; Weintraub and Burn, 2011). Further, as mentioned, the medications used to treat symptoms such as depression and psychosis developed for the treatment of these symptoms in younger patients, are not as affective in treatment these symptoms in older patients and less effective in treating patients with neurodegenerative diseases and these symptoms (Gauthier et al., 2010; Connolly and Fox, 2012).

Functional imaging studies demonstrated changes in neural circuitry in frontal cortices, including dorsolateral prefrontal cortex, orbitofrontal cortex, or anterior cingulate cortex of

depression in AD. In PD, frontal-basal ganglia circuits have been implicated in depressive symptoms. Neurochemical imaging studies have elucidated serotonergic and dopaminergic mechanisms of NPS in AD and PD. Further, interactions between neurotransmitter systems that can be imaged with PET may be more informative mechanistically and with respect to treatment development (Smith et al., 1997). Thus, this may explain why therapeutic strategies for late-life depression may be less effective in depression in AD and PD and other mechanisms may be more effective, such as receptor modulators (e.g. 5-HT4 agonists or D2 stabilizing medications). Future studies to elucidate the relationship between neurodegenerative pathology (eg. beta-amyloid deposition, tau and lewy bodies) and neurochemical systems that combined PET radiotracers in the same patients would also have important implications for the understanding of the neurobiology of NPS in neurodegenerative disease and may inform the development of more effective treatments.

7. Summary and Future Directions

The present review focused on molecular imaging studies of neurochemical and neuropathological mechanisms in AD and PD, with a focus on studies of NPS associated with these neurodegenerative diseases. In cases in which NPS were not evaluated relative to potentially relevant molecular targets, the imaging data were described and the potential relevance to NPS was discussed. In summary, neuroimaging studies of NPS have shown greater involvement of the neural circuitry affected in AD and PD, as well as greater deficits in dopaminergic and serotonergic systems, the most widely studied systems in these neurodegenerative diseases. A systematic investigation of specific NPS relative to neurochemical deficits in AD and PD has not been performed and is critically needed in order to determine whether the neurobiology of specific NPS such as depression, anxiety and apathy is similar or different between AD and PD. In AD, higher striatal D2 receptors have been associated with delusions and wandering behavior, which may be due to lower dopamine concentrations and higher striatal D2 receptors. Greater global NPS is associated with lower striatal D2 receptors and apathy is associated with lower dopamine transporters (section 3.1). In PD, lower striatal dopamine metabolism, dopamine transporters and D2 receptors are associated with depression and lower dopamine transporters are also associated with anxiety (section 5.1). Based on the available data, NPS in AD and PD may be associated with a greater dopaminergic deficit.

In AD, the serotonergic deficit involves a decrease in the serotonin transporter, 5-HT2A and 5-HT1A receptors. The serotonin transporter is further decreased in AD patients with depression. In PD, a decrease in both the serotonin transporters and 5-HT1A receptors are observed. Depression in PD is associated with higher serotonin transporters and lower 5-HT1A receptors. Visual hallucinations are associated with higher 5-HT2A receptors (section 5.2). Thus, with respect to depression, lower serotonin transporters are observed in AD and higher serotonin transporters are observed in PD. It is important to note that secondary depression in other conditions, including HIV, is associated with an increase in serotonin transporters (Hammoud et al., 2010). The differences between AD and other conditions, including PD may be due to the possibility that the degeneration of the serotonin system is more severe in AD than other neurodegenerative disorders. Understanding the significance of the relationship between depression and change in the serotonin transporter may have

implications for why the SSRIs are not effective in treating depression in these conditions and for identifying other neurochemical targets that may be more effective. NPS may be a target for prevention strategies, in normal aging or in prodromal states of AD or PD, if the underlying mechanisms were better understood. This is particularly important as many neurodegenerative diseases first present with mood or other NPS. Important areas of focus include studies to investigate neurobiological mechanisms of risk genes for psychiatric and neurodegenerative conditions identified in neuropsychiatric diseases, multi-modality imaging studies to understand changes in neural circuitry for mood, reward and cognition relative to changes in neurochemistry and combined radiotracer studies to evaluate alterations in neurotransmitter interactions (e.g. dopamine and serotonin modulation of other monoamines, acetylcholine, glutamate) or to evaluate the relationship between neurochemical changes and other aspects of neuropathology that may be associated (Liu et al., 2008). Similar considerations and priorities apply to studying prodromal states of neurodegenerative diseases such as MCI. The clinical management of NPS in AD and PD is a major challenge in geriatric neuropsychiatry. The medications developed and used to treat such symptoms as depression, psychosis and agitation in younger patients are less effective or ineffective in treating these symptoms in AD and PD. Even in the early stages of disease, monoamines and other neurotransmitter systems are substantially affected (e.g. serotonin, dopamine, norepinephrine) to a much greater extent than in younger patients. In addition to greater neurochemical changes, the neuropathology observed in AD and PD disrupts the function of cortical-cortical and cortical sub-cortical networks. In the development of more effective medications for NPS in AD and PD, the loss of receptors and transporters must be interpreted within the context of changes in neurotransmitter function, assessed, for example, by measuring the change in glucose metabolism or receptor availability (Smith et al., 2011; Volkow et al., 1994). In fact, the metabolic effects of acute drug interventions on metabolism have been correlated with subsequent treatment response in some studies, that indicates that the acute brain response to medication may have clinical implications in identifying treatment responders and non-responders (Smith et al., 2011). With respect to identifying targets for more effective treatments for NPS, possible mechanisms are neuroreceptor modulators that are in development that have mechanisms other than the approved psychotropic medications (e.g. 5-HT4 partial agonists and monoamine stabilizers; Brodney et al., 2012; Steensland et al., 2012; Jorge et al., 2008) as well as neural circuitry based interventions such as rTMS. In addition, molecular imaging studies can be used to evaluate drug occupancy, dosing and symptom/side effect relationships and to determine whether lower doses of psychotropic medications that may be safer, may also show comparable target occupancy. In developing more effective treatments for the clinical management of NPS in AD and PD, an understanding of the neurobiological mechanisms using molecular imaging is critical.

Acknowledgments

Supported in part by National Institute of Health/National Institute of Mental Health: RO1 MH 086881(GSS) and National Institute of Health/National Institute on Aging: K23AG044441 (GMP), AG038893 (GSS) and AG041633 (GSS).

Abbreviations

NPS	Neuropsychiatric symptoms
AD	Alzheimer's disease
PD	Parkinson's disease
MCI	Mild cognitive impairment
DLB	Dementia with Lewy bodies
PET	positron emission tomography
SPECT	single photon emission computed tomography
MRI	magnetic resonance imaging
SSRIs	selective serotonin reuptake inhibitors
SNRIs	serotonin and norepinephrine reuptake inhibitors
ICD	impulse control disorder
5-HT	5-hydroxytryptamine
5-HIAA	5-hydroxyindole acetic acid
MMSE	Mini Mental State Examination
CSDD	Cornell Scale for Depression in Dementia
BPRS	Brief Psychiatric Rating Scale
NPI	Neuropsychiatric Inventory
rCBF	regional cerebral blood flow
nBM	nucleus Basalis of Meynert
ChAT	choline acetyltransferase
TSPO	translocator protein
PBR	peripheral benzodiazepine receptor
DBS	deep brain stimulation
rTMS	repetitive transcranial magnetic stimulation
RCTs	randomized controlled trials
DLPFC	dorsolateral prefrontal cortex
SMA	supplementary motor area
HIV	human immunodeficiency virus

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Highlights

- Neuropsychiatric symptoms have a negative impact on disability and disease course.
- Treatment of NPS in younger patients is not effective in AD and PD.
- Neuroimaging of NPS has shown greater impairment of AD and PD neural circuitry.
- Greater deficits in dopaminergic and serotonergic systems are associated with NPS.
- Further *in vivo* neurochemical and neuropathology studies are needed.