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Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits?

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Abstract

Neuropsychiatric symptoms (NPS) are very common in Alzheimer's disease (AD), particularly agitation, apathy, depression, and delusions. Brain networks or circuits underlying these symptoms are just starting to be understood, and there is a growing imaging and neurochemical evidence base for understanding potential mechanisms for NPS. We offer a synthetic review of the recent literature and offer hypotheses for potential networks/circuits underlying these NPS, particularly agitation, apathy, and delusions. Agitation in AD appears to be associated with deficits in structure and function of frontal cortex, anterior cingulate cortex, posterior cingulate cortex, amygdala, and hippocampus, and may be associated with mechanisms underlying misinterpretation of threats and affective regulation. Apathy in AD is associated with frontal cortex, anterior cingulate cortex, posterior cingulate cortex, as well as orbitofrontal cortex, and inferior temporal cortex, and may be associated with mechanisms underlying avoidance behaviors.

Keywords

Alzheimer's disease; Neuropsychiatric symptoms; Agitation; Apathy; Depression; Delusions; Anterior cingulate cortex; Posterior cingulate cortex; Orbitrofrontal cortex; Inferior temporal cortex; Insula; Amygdala; Neuroimaging; Functional imaging

1. Background

Alzheimer's disease (AD) is the leading neurodegenerative disease of aging, affecting an estimated 5.2 million patients in the U.S. with a prevalence predicted to triple by the year 2050 (Alzheimer's Association, 2014). AD is a major cause of disability and caregiver burden; current treatments are not effective in slowing cognitive and functional decline. AD affects not only cognition but also mood and behavior, with most AD patients developing neuropsychiatric symptoms (NPS) (Steinberg et al., 2008). The most common NPS in AD are agitation, apathy, depression, and psychosis (particularly delusions) (Lyketsos et al., 2000, 2002).

NPS add to patient disability and caregiver burden, as well as being associated with more rapid progression to severe dementia and death (Peters et al., 2015). NPS can occur at any

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stage of AD but in general become more prevalent as dementia severity, hence also brain damage from AD, increases. There are no FDA-approved medications for NPS in AD yet psychotropic medications are often prescribed off-label with varied success. There is growing evidence supporting the e3cacy of novel medications for NPS in AD including citalopram for agitation (Porsteinsson et al., 2014), methylphenidate for apathy (Rosenberg et al., 2013), in addition to established evidence supporting the e3cacy of antipsychotics for psychosis (Sultzer et al., 2008). Antidepressants have not proved effective for depression in several well-powered negative trials (Banerjee et al., 2011; Rosenberg et al., 2010). One of the reasons for the relative paucity of therapeutic options is the limited understanding of the etiopathogenesis of NPS in AD, in particular their links to the AD brain disease.

Recent application of more precise neuroimaging and neurochemistry methods have led to a clearer understanding of the relationship between the underlying AD brain disease and its clinical manifestations in the form of NPS. A limited but growing base of evidence now allows the development of hypotheses about brain mechanisms underlying NPS in AD. In this paper we begin by identifying brain regions for which changes in structure and/or function are associated with NPS. As several spatially disparate regions are associated with NPS, we hypothesize that these are in fact linked functionally as brain “networks” or “circuits,” terms that we use interchangeably. While most of the evidence is associative at this point, the idea that regions associated with NPS are part of functional networks (circuits) is our central hypothesis.

There is increasing evidence that NPS are caused by dysfunction in specific networks (Dichter et al., 2014; Greicius, 2008; Grupe and Nitschke, 2013; Hamon and Blier, 2013; Menon, 2011; Price and Drevets, 2010; Price and Drevets, 2012; Tromp et al., 2012; Uhlhaas, 2013), with overlap between proposed networks and conditions. This is consistent with findings contrasting circuit disruption in AD vs. frontotemporal dementia (FTD). For example, early in its course the AD brain disease appears to disrupt the default mode network (DMN), a circuit that is active when a person is not focused on external stimuli and the brain is in a state of wakeful rest. The DMN likely includes posterior hippocampal, cingulate, temporal, and parietal regions. This disruption is thought to account for some of the cognitive impairments of early AD, executive dysfunction in particular. In contrast, behavioral variant fronto-temporal dementia (bvFTD), where behavioral symptoms predominate, tends to affect areas implicated in the salience network (SN) including anterior insula, anterior cingulate cortex (ACC), medial/orbital prefrontal cortex, striatum, thalamus, and amygdala, regions implicated in social and emotional processing (Zhou and Seeley, 2014). There appears to be strengthened SN connectivity in AD associated with decreased DMN connectivity, and the converse appears to be the case for bvFTD (Zhou and Seeley, 2014).

Applying a similar approach to understanding NPS, we propose that variability of brain network disruption by the AD brain disease accounts for variability in NPS phenotypes. To support this idea we review the imaging and neurochemical literature relevant to this hypothesis. Our approach is synthetic, not systematic, as the literature is sparse rendering direct comparisons between studies challenging. We focus on literature of the last 10 years with selected older, relevant studies. To limit heterogeneity we focus on AD, excluding

studies of other dementias, even though this reasoning probably applies to other conditions as well such as bvFTD. We emphasize replicated findings where available. Inevitably, we address methodological issues particularly relating to phenotyping.

2. Results

Agitation is at once the most problematic behavior for AD caregivers, yet among the most challenging to define and measure. While investigators generally agree on the presence and importance of the symptom of agitation only recently has there emerged consensus on the definition of a syndrome: a 2014 consensus statement from the International Psychogeriatric Association presents a syndromic definition of agitation (Cummings et al., 2015). The most widely used NPS measure in AD research is the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) with different versions administered to caregivers, and patients, as a structured interview (NPI or NPI-NH) or questionnaire (NPI-Q) (Kaufer et al., 2000). NPI rates frequency, severity, and caregiver distress related to 12 NPS domains. Agitation/Aggression is one of the domains: most studies have estimated the severity of NPI Agitation/Aggression as either a continuous or dichotomous (cutoff) measure of agitation. As agitation and aggression are conflated, an evolved NPI-Clinician Version, NPI-C (de Medeiros et al., 2010), differentiates the two. Another widely measure of agitation in AD is the Cohen–Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield, 1996), assessing a broad range of agitated behaviors. CMAI is more finely descriptive of agitation than a single NPI domain, but less widely used because of the time needed for administration. An alternative measure used in some of the studies we review is the Present Behavior Examination (PBE) which has four domains (overactivity, psychosis, aggressiveness, and depression) (Hope and Fairburn, 1992).

Table 1 summarizes recent neuroimaging studies of agitation in AD. Seven reports have applied magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), [^{99m}Tc]-HMPAO single-positron emission tomography (SPECT) assessment of perfusion, [^{18}F] florbetapir PET imaging of amyloid plaques, or resting state fMRI to study agitation. While there is no complete concordance between the results there are several areas of overlap that merit attention. Agitation was consistently associated with volume loss in several specific brain areas including frontal cortex (Hu et al., 2015; Trzepacz et al., 2013b), anterior cingulate cortex (ACC) (Bruen et al., 2008; Trzepacz et al., 2013b), posterior cingulate cortex (PCC) (Hu et al., 2015; Trzepacz et al., 2013b), insula (Bruen et al., 2008; Hu et al., 2015; Trzepacz et al., 2013b), amygdala (Trzepacz et al., 2013b), and hippocampus (Trzepacz et al., 2013b). There were no neurochemical imaging studies of agitation. The sole SPECT perfusion study (Hirono et al., 2000) linked agitation with hypoperfusion in left anteriotemporal, right parietal, and bilateral dorsofrontal cortex. In a study using DTI Tighe et al. (2012) reported that NPI Irritability (but not Agitation/Aggression) was associated with lower fractional anisotropy (FA) (suggesting decreased WM integrity) in ACC. Using resting state functional connectivity methods, Balthazar et al. (2014) reported an association between a composite NPI measure of “hyperactivity” and increased connectivity with right ACC and insula, which they interpret as stronger connectivity in the right salience network (Menon, 2011).

Several common themes emerge from these results. First, there are structural and functional deficits in a number of brain regions that are also implicated in the distribution of core AD pathology including PCC and hippocampus (Mattsson et al., 2014), suggesting an association between the core processes of AD disease progression and agitation. There are also structural and functional deficits in brain regions associated with emotional regulation (amygdala) and salience (insula) (Zhou and Seeley, 2014). These suggest that agitation in AD arises out of deficits in regulating emotional responses and/or attentional resources, and may involve deficits in problem-solving. These may constitute two different mechanisms for agitation in AD, one due to deficits in affective regulation (emotional responses) and the other due to deficits in executive function (problem-solving).

Table 2 summarizes neurochemical findings on agitation in AD. Three studies used brain autopsy specimens assessing associations with the PBE domains of overactivity and aggressiveness (Garcia-Alloza et al., 2005; Guadagna et al., 2012; Minger et al., 2000). While the PBE domains are not identical to the more commonly used NPI, both of these domains appear similar to NPI assessed Agitation/Aggression. All three studies concur: overactivity and/or aggressiveness were associated with *decreased* cholinergic markers, particularly in frontal and temporal cortex, and with *decreased* serotonin and serotonin metabolites. Two studies concur that agitation was associated with higher levels of tau and phosphorylated tau (phospho-tau), association with decreased PB2A enzymatic activity (PB2A is a tau phosphatase) in frontal cortex. This further links agitation to core aspects of AD pathology. There is overlap between the neurochemical and anatomic changes associated with agitation in AD. In AD, neurofibrillary tangles are seen early in the nucleus basalis of Meynert with cholinergic projections to a number of regions implicated in agitation including cingulate cortex, as well as in amygdala which is similarly implicated (Mesulam, 2013). Similarly, AD progression is associated with loss of serotoninergic neurons in the raphe and with their cortical projections, notably to frontal cortex and amygdala (Rodríguez et al., 2012). Degeneration of serotonin pathways may also diminish cholinergic neurotransmission (Rodríguez et al., 2012). Thus the anatomy of neurochemical changes associated with agitation in AD fits partially with the functional and structural imaging evidence.

2.1. Apathy in AD

Apathy, a common symptom of AD, involves decreased initiative and motivation, often subtyped into lack of initiative, lack of interest, and emotional blunting (Marin, 1991; Robert et al., 2009). There is great interest in apathy as a modulator of patient and caregiver burden in AD, but given its conceptual status as a mix of cognitive and mood symptoms there have been challenges in defining apathy in AD. There is consensus that lack of motivation is at the core, but it has been harder to characterize the role of introspection and patient report of inner feelings vs. the role of observed behaviors. Robert et al. (2009) proposed novel diagnostic criteria for apathy which have been most widely used in recent studies. These can be summarized as lack of motivation associated with lack of: (1) goal-directed behavior (either spontaneous or in reaction to the environment); (2) goal-directed cognitive activity (similarly, either spontaneous or in reaction to the environment), frequently manifested as loss of interest, and/or (3) spontaneous or reactive emotional

expression, frequently characterized as ‘emotional blunting.’ These criteria integrate the idea of lack of spontaneous behaviors and emotions with diminished reactivity to the environment. Instruments used to measure apathy severity are less well validated than those for agitation: they include the Apathy Evaluation Scale (AES) (Marin et al., 1991), Apathy Inventory (AI) (Robert et al., 2002), and Lille Apathy Scale (Sockeel et al., 2006).

Table 3 summarizes research that applied neuroimaging to the study of apathy in AD. While there are examples of discordant findings, and some null findings, substantial regional overlap and anatomic themes arise out of this literature. First and foremost, apathy in AD is associated with damage to the ACC as evidenced by decreased structural integrity or perfusion of the ACC, as well as with increased amyloid burden globally (Marshall et al., 2013) *especially* in ACC. Structural imaging studies report volume loss in ACC, including reduced gray matter volume (Apostolova et al., 2007; Bruen et al., 2008; Stanton et al., 2013) and cortical thinning (Tunnard et al., 2011). Similarly apathy is associated with decreased perfusion in ACC (Benoit et al., 2004; Lanctôt et al., 2007; Robert et al., 2006), decreased ACC white matter integrity by DTI (Hahn et al., 2013; Kim et al., 2011; Ota et al., 2012) and increased amyloid burden in right ACC (Mori et al., 2014). Apathy is also associated with decreased PCC metabolism (Delrieu et al., 2015). There are also links between apathy and volume loss and/or cortical thinning in frontal cortex (Apostolova et al., 2007; Bruen et al., 2008; Stanton et al., 2013; Tunnard et al., 2011), though there is no strict concordance on the specific regions of frontal cortex which include medial, lateral, and orbital regions. Apathy is further associated with greater amyloid burden in bilateral frontal cortex (Mori et al., 2014), reduced orbitofrontal metabolism on the left (Holthoff et al., 2005) or right (Lanctôt et al., 2007), and reduced connectivity in left-sided functional connectivity with frontal cortex (Baggio et al., 2015).

Two studies report an association of apathy with decreased insula volume (Moon et al., 2014; Stanton et al., 2013) although they disagree on whether this is bilateral or unilateral. Two studies note an association of apathy with decreased inferior temporal cortical (ITC) thickness (Donovan et al., 2014; Guercio et al., 2015). Of the two reports involving neurochemical imaging, one reported decreased bilateral putamen dopamine transporter density (David et al., 2008) while the other reported no association with D2/D3 dopamine receptor density (Reeves et al., 2009). These findings are of particular importance since a stimulant known to enhance brain dopamine release (methylphenidate) was efficacious in improving two of three apathy outcomes in a 6-week randomized, masked clinical trial (Rosenberg et al., 2013).

Two studies have endeavored to map specific subdomains of apathy (i.e., reduced initiative, emotional blunting, or lack of initiative) to neuroimaging findings in specific brain regions (Benoit et al., 2004; Stanton et al., 2013), with the only notable finding being that reduced initiative was associated with volume loss in ACC. A study of resting-state connectivity using functional MRI (fMRI) reported an association of apathy with reduced connectivity in left-sided circuits, predominantly involving limbic striatal and frontal territories (Baggio et al., 2015).

A number of intriguing findings are not well replicated or frankly contradictory, including an association of apathy with *decreased* frontal and temporal perfusion (Kang et al., 2012; Robert et al., 2006), *increased* hippocampal and temporal perfusion (Lanctôt et al., 2007), decreased caudate and putamenal volume (Bruen et al., 2008), decreased WM integrity in thalamus and parietal cortex (Ota et al., 2012), and failure to activate the amygdala on a "sad" fMRI task (Zhao et al., 2014). There is one study of FDG-PET changes longitudinally during an open-label trial of galantamine; galantamine treatment was associated with a slower rate of decrease in metabolism of the putamen (Mega et al., 2005).

We could only find one neurochemical study of apathy in AD. Skogseth et al. (2008) examined CSF from 32 subjects with AD and assayed for tau, phospho-tau, and $A\beta_{1–42}$. Apathy was assessed on the NPI-Apathy domain. Apathy severity was associated with higher levels of CSF tau and phospho-tau but not CSF $A\beta_{1–42}$. Since tau and phospho-tau are considered to be markers of downstream neurodegeneration in AD (Jack et al., 2013), this suggests that apathy is associated with core AD neurodegenerative processes.

2.2. Delusions in AD

Psychosis is generally defined by the presence of delusions and/or hallucinations. Delusions are defined as a "fixed false belief" and occur in many psychiatric disorders including schizophrenia, bipolar disorder, and psychotic depression. Delusions are a common NPS of AD, with a 5-year period prevalence of >50% in the longitudinal Cache County study (Steinberg et al., 2008).

Relevant imaging results are summarized in Table 4. Two studies (Koppel et al., 2014; Mega et al., 2000) grouped delusions and hallucinations together as "psychosis"; the remainder only studied delusions. Most of these studies did not attempt to dissociate delusions from agitation, and it seems unlikely that they examined "pure" delusions; for example, in one large cohort it was reported that delusions overlapped broadly with many symptoms of agitation (Rafii et al., 2014).

With these caveats, common themes still emerge. Delusions were associated with decreased gray matter (GM) volume, perfusion or metabolism in frontal cortex and ACC (Bruen et al., 2008; Koppel et al., 2014; Mega et al., 2000; Nakaaki et al., 2013; Rafii et al., 2011; Sultzer et al., 2003; Whitehead et al., 2012). Three studies localized these findings to orbitofrontal cortex, lateralized to right (Nakaaki et al., 2013), left (Whitehead et al., 2012), or bilaterally (Koppel et al., 2014). Others localized to dorsolateral frontal (Mega et al., 2000; Sultzer et al., 2003) or inferior frontal cortex (Nakaaki et al., 2013; Sultzer et al., 2003). Delusions were also associated with decreased perfusion in right anterior insula (Matsuoka et al., 2010) and decreased GM volume in left insula (Nakaaki et al., 2013). Less consistent are reports of decreased left striatal perfusion (Mega et al., 2000), or increased right lateral orbitofrontal cortical metabolism (Sultzer et al., 2003). One neurochemical study with raclopride PET imaging found an association between delusions and increased D2/D3 receptor density (Reeves et al., 2009). Lateralization findings were inconsistent, with two studies localizing to right (decreased right-sided metabolism (Sultzer et al., 2003) and decreased GM volume of right ACC, PCC, and orbitofrontal cortex (Nakaaki et al., 2013), while others localized to the left (Whitehead et al., 2012).

Hence, the most prominent themes are the association of delusions with structural and functional deficits in ACC and frontal cortex, with varied reports of localization to inferior frontal, dorsolateral frontal, and or orbitofrontal cortex. There is additionally implication of deficits in insula as well. These findings have quite a bit of overlap with those involving agitation, and could well reflect the co-occurrence of delusions with agitation. As well, they suggest that delusions are associated with core AD neurodegenerative processes along, especially with deficits in salience and the ability to focus brain resources to cope with emotionally charged states.

2.3. Depression in AD

Depressive symptoms are very common in AD, and an important focus for treatment though recent antidepressant trials have reported null results (Banerjee et al., 2011; Rosenberg et al., 2010). Major depressive disorder has been extensively studied as a possible disorder of neurocircuitry (Posner et al., 2013), but there are very few published neuroimaging data involving depression in AD. Zahodne et al. (2013) examined the association of NPI-Q Depression with GM volumes and cortical thickness in 334 subjects with MCI in the Alzheimer's Disease Neuroimaging Initiative (ADNI). They found Depression to be associated with reduced entorhinal cortical thickness at baseline and with accelerated atrophy in ACC. Hu et al. (2015) reported on a similar ADNI cohort of 202 subjects with MCI and 85 with AD, and found that NPI-Q Depression was associated with decreased GM volumes in left middle frontal cortex. The sole CSF study examined monoaminergic neurotransmitters, metabolites, and amino acids in 202 AD subjects reporting that lower CSF taurine was associated not only with depression, but also with overall NPS (Vermeiren et al., 2013). The same group published a brain autopsy series comparing 10 AD subjects with depression to 10 without using similar assays and found no significant differences between depressed and non-depressed patients (Vermeiren et al., 2014). While these four papers are intriguing there is insufficient evidence for generating hypotheses at this time.

3. Discussion

We review recent research that informs our understanding of brain mechanisms underlying neuropsychiatric symptoms of AD. We focus on agitation, apathy, delusions and depression as the most clinically important NPS. There is insufficient evidence for depression or psychosis to develop cogent hypotheses. Thus, we propose hypotheses for agitation and apathy. This is a small field and the results have significant overlap but quite a bit of disagreement as well. Given these results it is important to address methodological issues.

First, phenotyping is quite varied between studies, which likely accounts for much of the heterogeneity in results. There are different definitions of NPS and no consensus about the value of dimensional vs. categorical definitions. There is very little consideration of symptom overlap, especially important for making distinctions (or lack of distinctions) between agitation and psychosis, for example. Ample epidemiological data indicate that individual NPS rarely occur alone which is why we prefer to study individuals with predictable groups of symptoms (syndromes), namely agitation, psychosis, depression, and apathy (Geda et al., 2013). While, these groupings have been supported by most studies

(Johnson et al., 2011; Trzepacz et al., 2013a) others do not support this approach (Canevelli et al., 2013).

Second, there is a tendency to treat NPS as continuous (dimensional) variables to maximize statistical power. For the purpose of understanding circuits/networks, studies would be strengthened by treating NPS as categorical variables, i.e. analyze biomarker findings in case–control designs, using “clean cases” with minimal overlap of NPS based on consensus definitions. There are widely accepted definitions of agitation (Cummings et al., 2015), apathy (Robert et al., 2009), psychosis (Jeste and Finkel, 2000) and depression in AD (Olin et al., 2002), which provide a good starting point for studies examining association with imaging and other biomarkers of NPS in AD.

Third, there are similarly differing approaches to analyzing neuroimaging results. There is no overall consensus as to the relative merits of region of interest (ROI, hypothesis-based) analyses vs. voxel-based morphometry (VBM, unbiased) analyses of neuroimaging data with both techniques used widely. To perform whole brain analysis with no *a priori* hypothesis, voxel-based analysis is widely used. However, this approach tends to miss the widely distributed regions that show only small changes in parameters (Davatzikos, 2004) Structure-based voxel grouping, such as atlas-based analysis (ABA) (Oishi et al., 2009), is an attempt to overcome this limitation. It is based on the hypothesis that the white matter pathology of AD is structure-specific. The unique aspect of this approach is an implementation DTI atlas with fine delineation of DTI-visible white matter structures. If it is hypothesized the white matter pathology of AD is tract-specific, tract-based voxel grouping, such as Tract-Based Spatial Statistics (TBSS), can be applied (Nowrangi et al., 2015; Smith et al., 2006).

Though ROI approaches aim to identify structures implicated in certain cognitive or NPS phenotypes, there continues to be significant variance in detailing the boundaries of the ROIs. Moreover, the Alzheimer brain is often quite abnormal in structure compared to a normal brain, so “normalizing” to a template or atlas is not trivial. While this is certainly a challenge, there have been advancements in using atlas-based approaches to minimize inherent variability. The methodological detail of the image transformation and application to AD brains with substantial atrophy has been previously reported (Oishi et al., 2009) where high registration accuracy was demonstrated for both normal elderly and Alzheimer’s disease individuals.

Fourth, there are several areas of study for which the results do not tell a clear story, very possibly the result of underpowered studies and/or artifact. For example, although there are hints of laterality in the brain imaging findings, the results are often contradictory and it is premature to draw conclusions. Similarly, only one study notes a gender difference (Whitehead et al., 2012).

With these caveats we hypothesize mechanisms underlying agitation (Fig. 1) and apathy (Fig. 2) in AD. Agitated AD patients appear to have dysfunction in frontal cortex, ACC, orbitofrontal cortex, amygdala, and insula. These brain areas overlap with circuits that underlie inflated estimations of threat cost or probability, as well as maladaptive control of

responses (Grupe and Nitschke, 2013). Thus, agitation in AD involves miscalculation of the magnitude of potential threats, accompanied by increased threat attention and vigilance, and/or heightened reactivity to threat uncertainty (Grupe and Nitschke, 2013) (see their fig. 1a, 1b, and 1f). Seen this way, agitation is an emotionally hyperreactive state largely based on misinterpretation of threats ultimately rooted in cognitive deficits. Damage to these agitation circuits might cause a patient who forgot a routine event (resulting from damage to memory circuits) to conclude that it was an unexpected threat leading to overreaction and agitation. Similarly, damage to agitation circuits might cause a patient with agnosia to react to a family member as a stranger and become agitated. In this paradigm the agnosia or amnesia are caused by damage to different circuits while the reaction to these in specific settings results from damage to these agitation circuits.

Another way to consider agitation mechanisms is to revisit the resting state fMRI connectivity results between AD and bvFTD. Zhou et al. (2010) pointed out that in AD, DMN connectivity is decreased and SN is increased, while in bvFTD the opposite is true. The brain areas affected in agitation in AD are largely localized to SN (Fig. 1). Since there are similarities between agitated AD patients and bvFTD in that both may be disinhibited and demonstrate poor social judgment, one might hypothesize that agitation in AD is due to alterations in the balance of DMN and SN. The only published study on this reports *increased* SN connectivity in agitated AD patients, perhaps reflecting compensatory changes in network connectivity that account for reduction of DMN connectivity.

The neurochemical data on agitation in AD suggest it is associated with elevated tau and decreased acetylcholine and serotonin neurotransmission (all associated with the core neurodegenerative processes of AD). We have written before that since thalamocortical circuits (and indeed most circuits connecting deep brain structures to cortex) are inhibitory (Nowrangi et al., 2014), decreased serotoninergic and acetylcholinergic neurotransmission would imply less inhibition of cortex. Thus agitation may be an example of removing inhibitory input that ordinarily serves to control behavior to the cortical circuits associated with agitation. However, the current evidence does not clarify the temporal order of neurochemical changes vs. circuit disruptions, one may precede the other or they may be simultaneous processes.

We note that apathy in AD is associated with dysfunction in several structures overlapping with agitation (frontal cortex, ACC, orbitofrontal cortex and insula) as well as amygdala and (to a limited extent) striatum (Fig. 2). In Grupe et al.'s schematic, this overlaps with circuits that subsume behavioral and cognitive avoidance (Grupe and Nitschke, 2013). Certainly lack of interest, lack of initiative, and emotional blunting could be construed as manifestations of avoidance, as the patient seeks to avoid anxiety-provoking situations and thoughts. Although dopaminergic neurotransmission is thought to underlie many goal-directed behaviors including addiction, and there is evidence for the e3cacy of dopaminergic agents for apathy in AD (Rosenberg et al., 2013), there was no association between dopamine D2/ D3 receptor density and apathy in AD (Reeves et al., 2009). CSF tau was associated with apathy in AD, suggesting as before an association between apathy and the core neurodegenerative processes of AD.

Since most of the studies of delusions in AD did not exclude agitation, there is understandably much overlap between the imaging findings in these areas. We did identify several dysfunctional areas in delusional, but not agitated AD patients, including the parahippocampal gyrus, inferior frontal pole, right superior frontal cortex, putamen, left superior temporal, and claustrum. Based on current evidence it is not clear how these regions might fit together as a brain network. There is one report of delusions in AD being associated with increase dopamine receptor density; it is possible that dopaminergic neurotransmission is relatively enhanced as a secondary compensation for loss of serotonin and/or acetylcholinergic inhibition, and that dopamine to acetylcholine or serotonin imbalance might be behind the development of delusions.

It is increasingly evident that there is overlap between symptoms of neuropsychiatric illnesses and that our understanding of brain mechanisms needs to account for this overlap. It is similarly evident that one cannot map NPS to deficits in single brain regions or to global neurochemical changes in the brain. Rather alterations in brain circuitry most likely mediate the association of brain neurodegenerative pathology with behavior and emotion. These associations are being explored under the conceptual framework of Research Domain Criteria (Cuthbert and Insel, 2013; Insel et al., 2010). Our review of the data on the biology of NPS in AD suggests specific circuit alterations underlying the link of AD pathology with NPS, with these associations being particularly compelling for agitation and apathy in specific circuits (Fig. 1 and Fig. 2) given intriguing overlap with relevant brain circuits (Grupe and Nitschke, 2013). In the case of agitation, these circuits underlie inflated estimations of threat cost or probability, as well as maladaptive control of responses. For apathy, these circuits underlie behavioral and cognitive avoidance. Both these associations make clinical sense: agitated AD patients indeed appear to overestimate and overreact to threats and be unable to modulate strong emotional responses, while apathetic AD patients tend to isolate and avoid social interaction.

We hypothesize that the occurrence of agitation and apathy in AD are subsumed by networks that underlie the anticipatory aspects of anxiety, and suggest common mechanisms between agitation in AD and anxiety throughout the lifespan. In this context it is significant that the SSRI citalopram, noted for its anxiolytic effects, has been recently reported to be an effective treatment for agitation in AD (Porsteinsson et al., 2014). We have previously proposed that circuits underlying neuropsychiatric disorders give rise to NPS either by intrinsic circuit dysfunction or by loss or aberrant regulation of circuits from ascending monoamine systems (Lyketsos et al., 2004). It is possible that these parallels of brain circuitry can translate into parallels for intervention development, including both pharmacologic and non-pharmacologic interventions. The proposed circuits might be interrogated with functional imaging such as resting-state or task-based fMRI, and could prove as useful biomarkers for development of novel interventions. While we have good data to suggest regions and structures that may be associated with a behavior or symptom, we are only beginning to understand how these are in fact “connected” at the white matter level. Ultimately, multi-modal approaches that identify both structural and functional integrity of white matter tracts between associated structures or regions will be especially elucidative.

We seek to better understand mechanisms of NPS not merely for their own sake but to better target new treatments. To date, successful medication trials have been re-purposing FDA drugs approved for similar (Porsteinsson et al., 2014) or dissimilar (Rosenberg et al., 2013) indications. While this method of drug discovery has the attractive feature of studying drugs with generally well-characterized safety profiles, it is inherently limited especially in terms of interpreting null results (Rosenberg et al., 2010). Understanding mechanisms of NPS may help us target new neurochemical mechanisms and better understand how non-pharmacologic and pharmacologic strategies synergize. Neurochemical and functional imaging measures may provide useful biomarkers of target engagement for proof-of-concept early phase intervention trials, while structural imaging is more likely to identify patients that likely to respond to a particular treatment. Additionally, understanding functional/structural network connectivity may help track **treatment response** for targeted drug therapy. For example, it is important in treatment development to know whether observed changes in networks are the result of reconstitution of deficient network function or reflect plasticity from recruitment of compensatory circuits. Thus, we propose that further study of NPS mechanisms will inform discovery of pharmacologic and nonpharmacologic strategies for treatment and help us attack this major public health problem.

Abbreviations

ABA	atlas-based analysis
ACC	anterior cingulate cortex
AD	Alzheimer's disease
ADNI	Alzheimer' Disease Neuroimaging Initiative
AES	Apathy Evaluation Scale
AI	Apathy Inventory
Amy	amygdala
bv-FTD	behavioral variant frontotemporal dementia
CMAI	Cohen-Mansfield Agitation Inventory
DMN	default mode network
DTI	diffusion tensor imaging
FA	fractional anisotropy
FC	frontal cortex
FDG-PET	[^{18}F] fluorodeoxyglucose positron emission tomography
FTD	frontotemporal dementia
fMRI	functional MRI
GM	gray matter
HC	hippocampus

ITC	inferior temporal cortex
MRI	magnetic resonance imaging
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory, Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
NPI-C	Neuropsychiatric Inventory, Clinician Version
NPS	neuropsychiatric symptoms
OFC	orbitofrontal cortex
PBE	Present Behavior Examination
PCC	posterior cingulate cortex
PET	positron emission tomography
phospho-tau	phosphorylated tau
PIB-PET	Pittsburgh Compound B positron emission tomography
ROI	region of interest
SPECT	[^{99m}Tc] HMPAO single-positron emission computerized tomography
SN	salience network
TBSS	Tract-Based Spatial Statistics
VBM	voxel-based morphometry
WM	white matter
WMH	white matter hyperintensities

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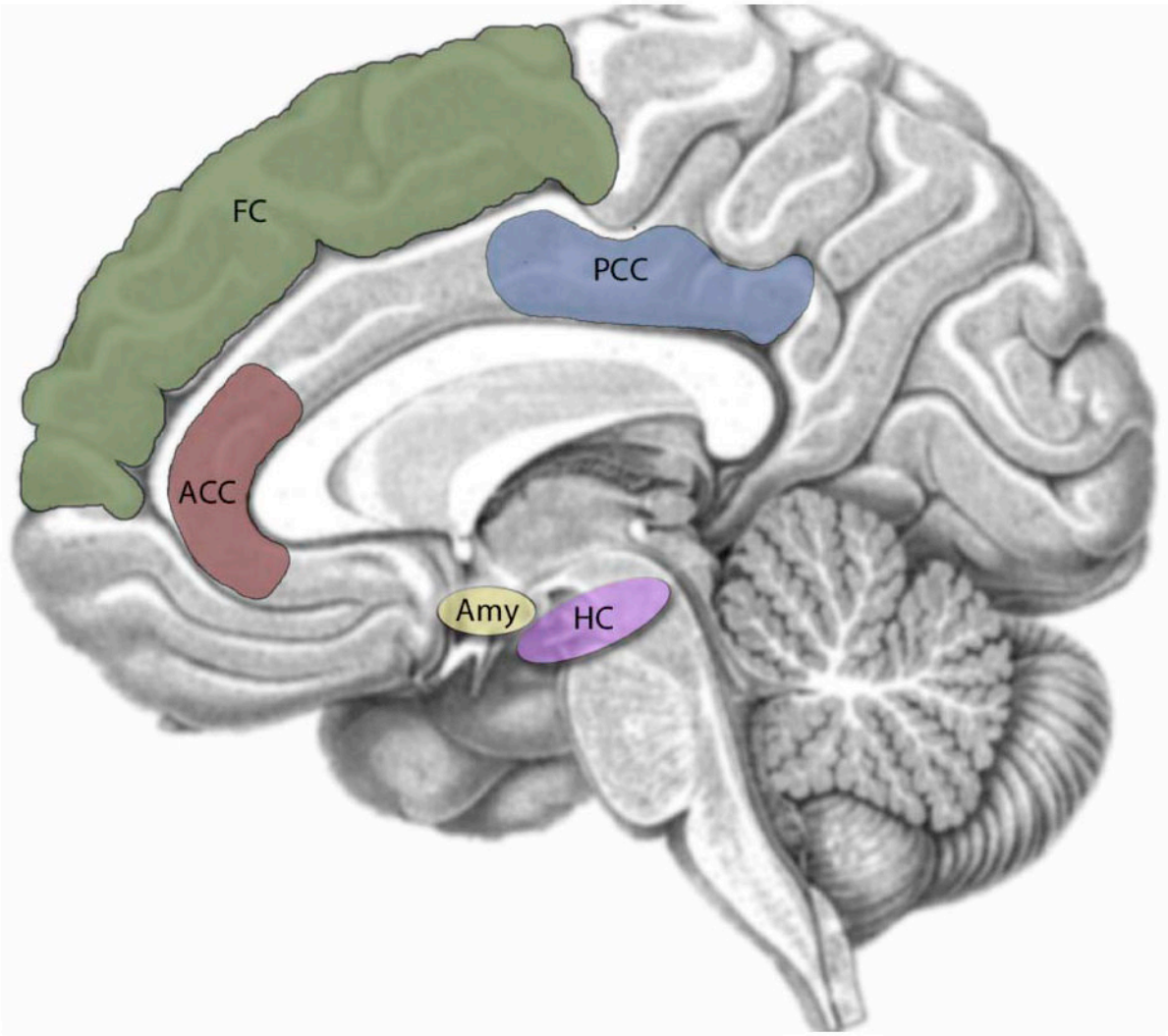

Fig. 1.
Brain regions implicated in agitation of AD network.

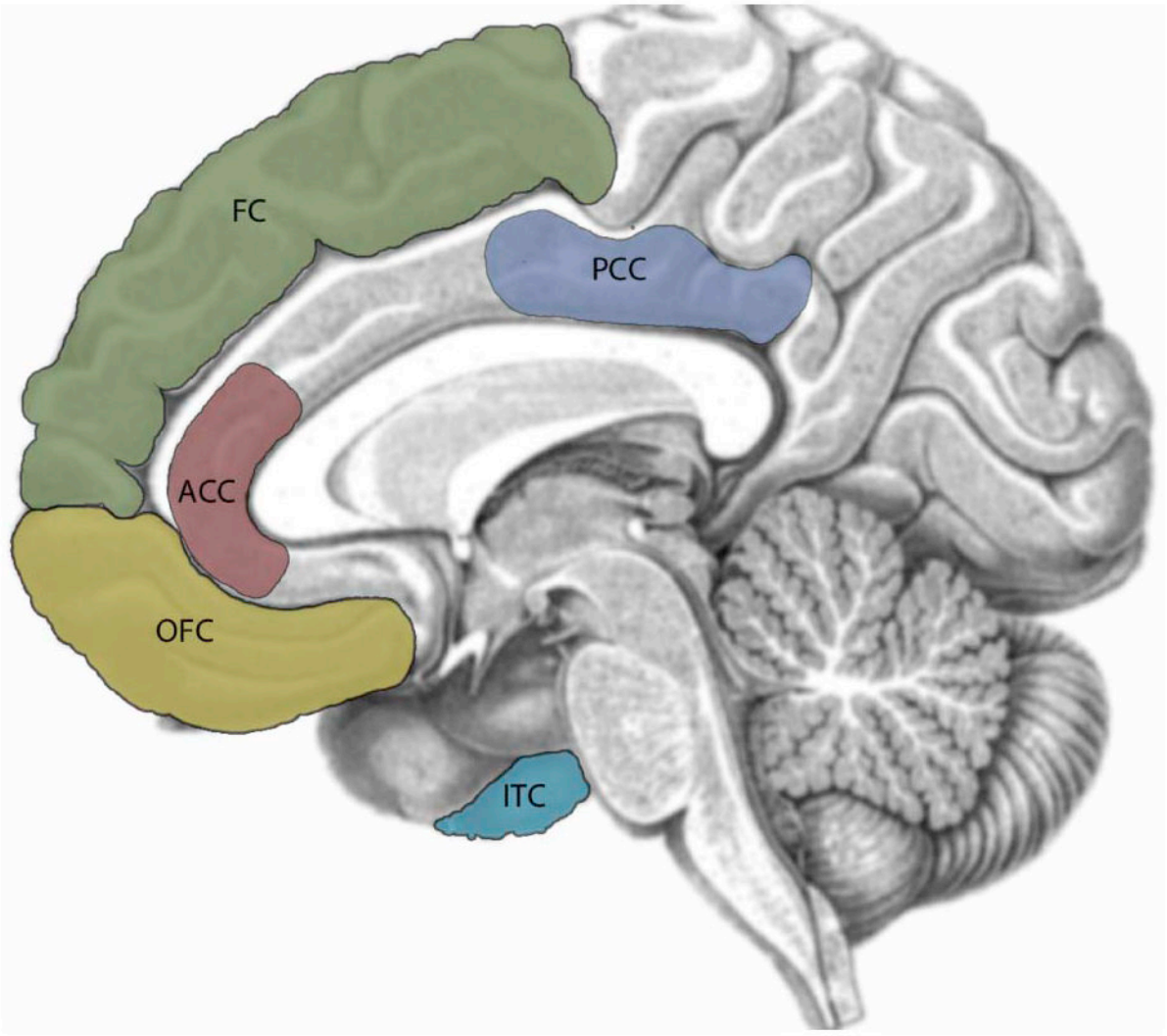

Fig. 2.
Brain regions implicated in apathy of AD network.

Table 1

Neuroimaging of Agitation in AD.

Reference	Imaging modalities	Population	Agitation measures	Agitation associated with	Comments
Hirono et al. (2000)	SPECT	AD (N = 20) 10 with agitation, 10 without agitation	NPI Agitation/Aggression	Decreased perfusion of left anterior temporal, bilateral dorsofrontal, and right parietal cortex	
Bruen et al. (2008)	MRI	AD (N = 31)	NPI-Q Agitation/Aggression	Decreased GM values in left insula, and bilateral anterior cingulate cortex	Parallel findings listed under Apathy and Delusions
Staekenborg et al. (2008)	MRI (Medial temporal atrophy, WM hyperintensities)	AD (N = 111)	NPI total and individual items (including Agitation/Aggression)	No associations	
Tighe et al. (2012)	DTI ROI analysis	MCI (N = 22) AD (N = 23)	NPI domains	NPI irritability associated with lower FA of anterior cingulate	Adjusted for MMSE
Trzepacz et al. (2013a, 2013b)	MRI	AD and MCI (N = 462)	NPI-Q Agitation/Aggression	Greater atrophy of frontal, insular, amygdala, cingulate, and hippocampus	Interpreted as atrophy of anterior salience network
Balthazar et al., (2014)	Resting state functional connectivity	AD (N = 20)	NPI hyperactivity composite subscale (sum of agitation, disinhibition, irritability, euphoria, and aberrant motor behavior scores)	Increased connectivity in right anterior salience network (specifically right ACC and right insula)	No associations between networks and affective symptoms, apathy, psychosis
Hu et al. 2015)	MRI	AD (N = 85) MCI (N = 202) HC (N = 131) ADNI	NPI Agitation/Aggression	GM atrophy in the left inferior frontal/insula, bilateral retrosplenial cortices, left middle frontal cortex	Replicated prior results from smaller cohort

Table 2

Neurochemistry of Agitation in AD.

Reference	Specimens	Population	Agitation measures	Neurochemical measures	Agitation Associated with	Comments
Minger et al. (2000)	Brain autopsy specimens	AD (N = 46)	PBE	Acetylcholine Choline Acetylacholinesterase Choline acetyltransferase 5HT 5HIAA DA DA receptors	Overactivity associated with lower ChAT in frontal and temporal cortex ChAT:DA and ChAT:D1 ratios in temporal cortex correlated negatively with aggressive behavior.	
Garcia-Alloza et al. (2005)	Brain autopsy specimens	AD (N = 22)	PBE	Acetylcholine Choline Acetylacholinesterase Choline acetyltransferase 5HT 5HIAA	Aggression associated with decreased cholinergic markers Overactivity associated with decreased 5HT and 5HIAA	Prospective study with autopsy
Guadagna et al. (2012)	Brain autopsy specimens	AD (N = 16)	PBE	Tau Phopho-tau	Higher ratio of phospho-tau to tau in frontal cortex, and agitation severity correlated with this ratio	PB2A (phosphatase for phospho-tau) expression lower in frontal cortex of subjects with higher phopho-tau
Bloniecki et al. (2014)	CSF	AD (N = 33) HC (N = 95)	CMAI	$A\beta_{1-42}$ Total tau Phospho-tau	Total tau and phospho-tau in AD only	No associations in entire cohort including HC

Table 3

Neuroimaging of Apathy in AD.

Reference	Imaging modalities	Population	Apathy measures	Apathy associated with	Comments
Benoit et al. (2004)	SPECT (perfusion)	AD (N = 30)	AI total and individual items	Less brain per-fusion in bilateral superior orbito-frontal gyrus, and left middle frontal gyrus. Lack of initiative associated with less perfusion in right anterior cingulate cortex. Lack of interest score associated with less perfusion in right middle orbitofrontal gyrus. Emotional blunting associated with less perfusion in left superior dorsolateral prefrontal cortex.	
Holthoff et al. (2005)	FDG-PET	AD (N = 53)	NPI-Apathy	Decreased left orbitofrontal metabolism	
Mega et al. (2005)	FDG-PET	AD (N = 19)	Longitudinal change in NPI-Apathy before and after open-label galantamine treatment	Decrease in apathy with treatment associated with increased (or less decrease) right ventral putamen metabolism	
Robert et al. (2006)	SPECT	AD (N = 31) 19 with apathy 12 without apathy	AI (lack of interest/ initiative)	Decreased right frontal and right inferior temporal perfusion. apathetic AD patients had less perfusion in the right anterior cingulate	Controlled for severity of depression
Apostolova et al. (2007)	MRI ROI brain volumes Cortical thickness	AD (N = 35) 17 with apathy 18 without apathy	NPI-Apathy	Atrophy of bilateral anterior cingulate, left medial frontal cortex, and left cingulate cortical thinning (trend level)	
Lanctôt et al. (2007)	SPECT	AD (N = 51) HC (N = 23)	NPI-Apathy 1	Lower perfusion in right orbitofrontal cortex and left anterior cingulate) Higher perfusion in bilateral hippocampus, bilateral middle medial temporal cortex, and left medial superior temporal gyrus	ROI analysis
Bruen et al. (2008)	MRI	AD (N = 31)	NPI-Q Apathy	Atrophy of bilateral anterior cingulate and frontal cortex, head of left caudate, bilateral putamen	ROI analysis
David et al. (2008)	DatScan SPECT (dopamine transporter-specific tracer)	AD (N = 16) DLB (N = 8)	AI	Decreased bilateral putamen dopamine transporter density	Adjusted for motor disturbance (UPDRS)
Reeves et al. (2009)	Raclopride PET (D2/D3 dopamine receptor)	AD (N = 23)	AI	No association	
Starkstein et al. (2009)	MRI GM volume WM hyperintensities (WMH)	AD (N = 79)	Apathy Scale	Greater frontal WMH Depression associated with greater right parietal WMH	No association of GM volumes with apathy or depression WMH volumes manually drawn
Kim et al. (2011)	DTI	AD (N = 51)	NPI-Apathy	Lower FA in left ACC	Controlled for depression severity and use of psychotropic medications
Tunnard et al. (2011)	MRI Cortical thickness	AD (N = 111)	NPI-Apathy	Thinner left caudal anterior cingulate cortex (ACC) and left lateral orbitofrontal cortex (OFC), as well as left superior and ventrolateral frontal regions	Automated MRI volumetrics

Reference	Imaging modalities	Population	Apathy measures	Apathy associated with	Comments
Kang et al. (2012)	SPECT	AD (N = 81)	NPI-Apathy	Decreased perfusion of right amygdala, temporal, posterior cingulate, right superior frontal, postcentral, and left superior temporal gyri	Associations quite distinct from associations with NPI-Depression
Ota et al. (2012)	DTI	AD (N = 21)	Apathy Scale	Lower FA values in the right anterior cingulate, right thalamus, and bilateral parietal regions	Controlling for age, education, and MMSE
Marshall et al. (2013)	PIB-PET (amyloid) FDG-PET (glucose uptake)	MCI (N = 24)	AES	Greater cortical PIB retention No association with FDG-PET uptake	
Hahn et al. (2013)	DTI	AD with apathy (N = 30) AD without apathy (N = 30)	AI	Lower FA in genu of the corpus callosum Apathy severity associated with lower FA in left anterior and posterior cingulate, right superior longitudinal fasciculus, corpus callosum and bilateral uncinate	Excluded NPI-Depression > 0
Stanton et al. (2013)	MRI VBM	AD (N = 17) PSP (N = 17)	AI Apathy defined by Robert criteria	Atrophy of the ventromedial orbitofrontal cortex and left insula Reduced initiative associated with atrophy of the anterior cingulate and ventrolateral orbitofrontal cortex Emotional blunting associated with atrophy of the left insula.	Combined AD and PSP for analyses
Donovan et al. (2014)	MRI cortical thickness CSF $A\beta_{1-42}$	AD, MCI, and HC (N = 1812 for MRI, 413 for CSF)	NPI-Q Apathy (change over time)	Decreased baseline inferior temporal cortical thickness No associations with CSF $A\beta_{1-42}$	Outcomes were longitudinal change in apathy
Zhao et al. (2014)	Task-based fMRI “sad” vs. “neutral” tasks	AD (N = 13) 7 with apathy 6 without apathy	AES-C Lille Apathy Scale Apathy defined by Robert criteria	Failure to activate amygdala with the “sad” task	
Mori et al. (2014)	PIB PET (amyloid) ROI	AD known to be PIB (+) (N = 28)	NPI-Apathy	Apathy severity associated with greater PIB retention in bilateral frontal and right anterior cingulate Presence of apathy associated with greater PIB retention in bilateral frontal cortex	
Moon et al. (2014)	MRI	AD (N = 40)	NPI-Apathy	Apathy and irritability associated with decreased volume of bilateral anterior insula and right posterior insula	Similar associations with NPI-Irritability
Delrieu et al. (2015)	MRI (volume) FDG-PET	MCI (N = 65) 11 with apathy, 54 without	NPI-Q apathy	Decreased posterior cingulate metabolism	no volumetric differences
Guercio et al. (2015)	MRI (cortical thickness)	MCI (N = 47) HC (N = 19)	AES-C	Lower inferior temporal cortical thickness	
Baggio et al. (2015)	Resting state functional connectivity	PD (N = 62) 25 with apathy 37 without apathy	Apathy Scale	Reduced connectivity in left-sided circuits, predominantly involving limbic striatal and frontal territories.	Controlling for cognitive performance

Table 4

Neuroimaging of psychosis in AD.

Reference	Imaging modalities	Population	Psychosis measures	Psychosis associated with	Comments
Mega et al. (2000)	SPECT VBM comparison	AD (N = 2010 with psychosis, 10 without psychosis	NPI Delusions and/or Hallucinations	Less perfusion in bilateral dorsolateral frontal, left anterior cingulate, and left ventral striatal regions along with the left pulvinar and dorsolateral parietal cortex	
Sultzer et al. (2003)	FDG-PET	AD (N = 25)	Neurobehavioral Rating Scale – Delusions	Delusions associated with decreased glucose uptake in right superior dorsolateral frontal cortex and inferior frontal pole increased glucose uptake in right lateral orbitofrontal region	Additional associations only on univariate analyses
Bruen et al. (2008)	MRI	AD (N = 31)	NPI-Q Delusions	Decreased GM density in the left frontal lobe, in the right frontoparietal cortex and in the left claustrum	
Reeves et al. (2009)	Raclopride PET (D2/D3 dopamine receptor)	AD (N = 23)	NPI-Delusions AI	Increased D2/D3 striatal receptor density	
Matsuoka et al. (2010)	SPECT	AD with delusions (N = 14) AD without delusions (N = 21)	NPI delusions	Delusion severity associated with less rCBF in the right anterior insula	But rCBF in the right anterior insula was not significantly decreased in patients with delusions
Nakaaki et al. (2013)	MRI Voxel-based morphometry	AD (N = 53) 18 developed delusions over 2-year followup	New onset NPI Delusions	Delusion severity associated with smaller bilateral parahippocampal gyrus, right posterior cingulate gyrus, right orbitofrontal cortex, bilateral inferior frontal cortex, right anterior cingulate, left insula.	
Whitehead et al. (2012)	MRI Regional brain volumes and cortical thickness	AD (N = 113)	NPI Delusions	Decreased cortical thickness in left medial orbitofrontal and left superior temporal regions only in women	
Rafii et al. (2014)	MRI	MCI and AD (N = 389)	Adverse event of “psychosis” including broad range of neuropsychiatric symptoms (12% of sample, N = 47) NPI	Longitudinal volume loss in lateral frontal, lateral parietal, and anterior cingulate gyrus	Broad overlap with agitation symptoms
Koppel et al. (2014)	FDG-PET	21 AD patients with incident psychosis vs. 21 AD patients with no onset psychosis 39 AD patients with psychosis at baseline vs. 39 AD patients with no psychosis at baseline ADNI	NPI-Q Delusions and/or Hallucinations	Current psychosis associated with decreased orbitofrontal metabolism no associations with incident psychosis	Psychosis associated with accelerated functional decline