

Noncognitive Behavioral Changes Associated With Alzheimer's Disease: Implications of Neuroimaging Findings

Jeff Victoroff, M.D., Feng V. Lin, Ph.D., Kerry L. Coburn, Ph.D., Samuel D. Shillcutt, Pharm.D., Ph.D., Valerie Voon, M.D., Ph.D., Simon Ducharme, M.D., M.Sc.

Alzheimer's disease (AD) is commonly associated with non-cognitive behavioral changes (NCBCs). The authors systematically reviewed whether neuroimaging has helped with understanding the pathophysiology, diagnosis, or management of NCBCs associated with AD, including depression, aggression or agitation, anxiety, apathy, psychosis, and sleep disorder. The authors identified dissociable neural substrates with multimodal imaging: depression implicates the lateral and superior prefrontal cortex; apathy and agitation implicate the dorsal anterior cingulate; psychosis implicates right lateralized

frontal and medial temporal areas; and anxiety implicates mesial temporal regions. Frontal white matter changes appear to underlie many NCBCs, emphasizing the preventative management of vascular risk factors. Further delineation of underlying neurocircuitry and pathophysiology in larger data sets might lead to biomarker identification for diagnosis and optimizing treatment targets.

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Alzheimer's disease (AD) is commonly associated with non-cognitive behavioral changes (NCBCs) (also known as “behavioral and psychiatric symptoms of dementia” or “behavioral and psychological symptoms of dementia”),¹ contributing to the heterogeneity of the disorder. Multiple types of NCBCs have been identified, including depression, aggression, agitation, hyperactivity, apathy, anxiety, psychosis, wandering, and sleep disorders.² These symptoms have important clinical implications affecting quality of life, increasing caregiver distress and cost of care, and precipitating institutionalization, and they may be associated with accelerated mortality.² That the behaviors can predate the onset of AD suggests that greater focus on the behaviors may facilitate the early diagnosis of neurodegenerative disease.² With growing awareness of NCBCs, the concept of AD is evolving, with some proposals that neuropsychiatric symptoms may be intrinsic to the disorder.³ The pathophysiological and psychological mechanisms underlying NCBCs remain poorly understood. Here we review whether neuroimaging has helped with understanding the pathophysiology, diagnosis, or management of NCBCs associated with AD. Our findings highlight common findings of frontal white matter changes underlying many NCBCs and more fine-grained dissociable neural substrates associated with NCBCs with multimodal imaging.

METHODS

The common NCBCs reported include depression, aggression, agitation, hyperactivity, apathy, anxiety, psychosis, euphoria, wandering, and sleep disorders. Since there were very few articles regarding euphoria and wandering, these NCBCs were not included. Given the overlap between aggression, agitation, and hyperactivity, we adopted this symptom cluster, as per van Linde et al.⁴

We focused on MRI (including functional MRI [fMRI]), magnetic resonance spectroscopy (MRS), and nuclear medicine imaging. Since MR imaging only became widely available in 1984, we confined our search to the last two decades. Search algorithms reported in the Appendix in Supplementary Materials were similar across NCBCs for MEDLINE and PsycINFO. Each two-investigator team reviewed the abstracts and, if judged equivocal, the full text was reviewed. Papers were included if 1) the subjects met clinical diagnostic criteria for possible or probable AD either by using 2011 criteria by McKhann et al.⁵ or by data regarding AD subjects that could be segregated for analysis, 2) the primary imaging technique was clearly identified, and 3) statistical analysis was presented. Results of the search are shown in Table S1 in the data supplement accompanying the online version of this article.

Depression

Depression is frequently encountered as a symptom accompanying dementia, and is thought to represent a risk factor for the cognitive decline from normal aging through mild cognitive impairment (MCI) to AD.⁶ In a rare longitudinal study following 639 independently living elderly subjects for 3 years, Verdelho et al.⁷ found that depression symptoms predicted cognitive decline independently from white matter hyperintensities (WMHs) or other structural changes. The picture is complicated, however, by a notoriously high prevalence of chronic late-life depression (LLD) among the cognitively normal elderly. In this section we explore two questions: What brain areas are implicated in depression in AD, and how does this correspond to LLD without dementia (e.g., vascular pathology in periventricular areas)?⁸ Table S2 in the online data supplement summarizes the critical findings.

Clark et al.⁹ found no relationship between major depressive episodes in AD and WMHs. However, within his patient sample, subsyndromal depressive symptoms were more prevalent among those with anterior WMHs. Furthermore, earlier-onset AD was associated with more WMHs and greater premorbid depression compared with later-onset AD, consistent both with a relationship between WMH and depression and also with depression being a risk factor for AD. These findings were confirmed and extended in a larger study¹⁰ of dementia patients and controls reporting that frontal WMHs, but not those in periventricular or basal ganglia areas, were associated with higher depression scores. Importantly, these findings were irrespective of dementia etiology, being present in patients with AD, vascular dementia (VaD), and dementia with Lewy bodies. Similarly, Mueller et al.¹¹ found depression to be associated with frontal WMHs in AD and VaD, which was dissociable from cognitive deterioration associated with gray matter atrophy. Other structural MRI studies have been equivocal, with Starkstein et al.¹² reporting apathy rather than depression associated with frontal WMHs while depression corresponded to right parietal WMH in AD patients. Some researchers have found no relationship between WMHs and depression symptoms in seemingly adequate samples of AD, VaD, mixed AD-VaD, and MCI patients.^{13,14} Thus, many, but not all, structural MRI studies show a relationship between frontal WMHs and depressive symptoms in AD, but not with periventricular changes more consistent with LLD.

Depression symptoms in AD patients also relate to cortical and hippocampal atrophy. Compared with AD patients without depression, those with depression symptoms show a variable pattern of additional cortical atrophy in prefrontal and temporal areas,¹⁵ the left middle frontal cortex,¹⁶ left temporal and parietal areas¹⁵, and the left inferior temporal gyrus,¹⁷ as well as right hippocampal atrophy.¹⁸ Additional thinning of parahippocampal regions may be contingent on antidepressant use.¹⁵ However, less medial temporal atrophy also has been reported.¹⁹

Functional changes accompany depressive symptoms in AD patients, in the form of hypoperfusion of the left prefrontal area,²⁰ left middle (dorsolateral) prefrontal region,²¹ left middle frontal gyrus,²² and the left callosomarginal area of the left frontal cortex,²³ and in dorsolateral and superior prefrontal cortex generally.²⁴ (In this last study region of interest, analysis further indicated hypoperfusion of bilateral superior and middle frontal gyri, and anterior cingulate gyri before atrophy correction, but following correction these changes became nonsignificant.) Although most studies report anterior perfusion deficits to accompany depression symptoms, a small study found no relationship between depressive symptoms in AD patients and perfusion in any frontal or cingulate area.²⁵

Depression-related hypometabolism of the dorsolateral prefrontal area²⁶ has been reported, as has decreased fMRI regional homogeneity of the right precentral gyrus, right superior frontal gyrus, right middle frontal gyrus, and right inferior frontal cortex.²⁷ Depression scores correlate positively with the choline/creatine ratio in the left dorsolateral prefrontal cortex and with the myo-inositol/creatine ratio in the cingulate gyri bilaterally.²⁸ In contrast, there appear to be no depression-related differences in 5-HT_{2A} receptor binding²⁹ or cortical amyloid-B.³⁰

The reported brain abnormalities accompanying depressive symptoms in Alzheimer disease and those seen in LLD alone are becoming increasingly similar as additional information becomes available.

Two decades ago, it was reported that neither early-onset nor late-onset depression patients differed from healthy controls in terms of regional brain atrophy.³¹ Although a smaller whole brain volume was reported,³¹ this was attributed to antidepressant use, as were later findings of relative hippocampal atrophy and a larger WMH volume.³² More contemporary reports have found that compared with healthy controls, elderly nondemented patients suffering from depression show hippocampal atrophy^{33,34} which is not as severe as in nondepressed AD patients.³⁵ Hippocampal atrophy may³⁶ or may not³⁷ predict subsequent dementia. In addition to hippocampal atrophy, LLD patients showed atrophy of the superior frontal gyrus, ventromedial frontal cortex, and precuneus.³⁸ However, elderly depressed patients matched to AD patients for hippocampal atrophy show additional atrophy of medial temporal lobe structures and anterior cingulate cortex but not posterior cingulate cortex or precuneus.³⁹

Temporal lobe perfusion deficits have been reported in LLD patients compared with both healthy controls and early-onset depression patients,⁸ which are associated with periventricular WM changes.⁴⁰ As with AD patients, LLD patients show no abnormalities of 5-HT_{2A} receptor binding²⁹

Hippocampal atrophy in cognitively intact LLD patients is less severe than in AD patients³⁵ and may represent a subclinical stage of a dementing process. Temporal lobe perfusion deficits^{8,40} are consistent with this picture. However,

atrophy of the superior frontal gyrus, ventromedial frontal cortex, and anterior cingulate cortex^{38,39} in LLD may correspond to the abnormalities accompanying depressive symptoms in AD patients.

The results of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies have been remarkably consistent in identifying metabolic and hemodynamic abnormalities in dorsolateral and superior prefrontal cortical areas that may correspond to the subcortical WMHs identified in most but not all structural MRI studies. These structural and functional cerebrovascular changes appear to be associated with, and may underlie, depressive symptoms in AD patients. This finding is highly relevant to both pathophysiology and prevention: aging-related cerebrovascular changes are potentially preventable, a common theme emerging across the NCBCs. Thus, it might be hypothesized that medical management of vascular risk factors may significantly reduce both the burden of dementia and comorbid depression.

Psychosis

Psychosis is defined as a loss of contact with reality and includes psychosis not otherwise specified (PNOS); delusions not otherwise specified (DNOS); delusions of misidentification (DMI); delusions with paranoid or persecutory content; other delusions, such as phantom boarder; hallucinations not otherwise specified; auditory hallucinations; or visual hallucinations. The most common diagnosis was PNOS.

There were three common study designs: 1) contrasting AD subjects with and without psychosis, 2) contrasting AD subjects with psychosis with normal controls, and 3) correlation studies of the severity of psychosis among AD subjects using dimensional psychosis assessment scales (e.g., Dementia Psychosis Scale, Neuropsychiatric Inventory). The most recurrent finding relied on psychosis's association with reduced cerebral blood flow (CBF) or metabolism in frontal regions. The psychosis's associations with regional or overall atrophy or white matter changes were inconclusive, but these structural changes tend to lateralize in the right hemisphere.

Table S3A in the online data supplement summarizes nine studies of brain structure. All three CT studies comparing AD patients with and without delusions showed asymmetric right>left atrophy. However, the MRI results were inconsistent, reporting either no association with atrophy⁴¹ or that DNOS were associated with right hippocampal atrophy.⁴² Among the other four (nonvolumetric) MRI studies, findings were mixed, including finding no association between delusions and atrophy, but an association between hallucinations and overall atrophy⁴³; delusions associated with decreased cortical thickness, but only among women⁴⁴; and visual hallucinations associated with occipital atrophy.⁴⁵

Table S3B in the online data supplement summarizes seven studies of WM Δ . One study employed CT, and the presence of WM Δ was not associated with psychosis frequency.⁴⁶ Six studies employed MRI. Three studies compared AD patients

with and without psychosis reporting either no association with WM Δ ,⁴³ an association between DMI and WM Δ ,⁴⁷ or an association between visual hallucinations and occipital periventricular caps.⁴⁸ The other two MR studies compared AD patient with and without WM Δ . The larger study (N=163) reported that WM Δ were associated with delusions⁴⁹; the smaller study (N=38) reported that WM Δ were not associated with delusions.⁵⁰

Table S3C in the online data supplement summarizes 15 studies of CBF and psychosis in AD. Fourteen of these employed SPECT, and one used ¹⁵O PET. Ten of these fourteen compared AD subjects with and without psychosis. Taken as a whole, the findings suggest that psychosis was associated with diminished CBF on the right more often than the left, particularly in the frontal and medial temporal lobe.⁵¹⁻⁵⁷ Table S3D in the data supplement summarizes the three studies using [18]fluorodeoxyglucose (FDG) PET,⁵⁸⁻⁶⁰ showing that DMI or PNOS tended to be associated with decreased metabolism in frontal or temporal regions.

Table S3E in the data supplement lists three studies with unique designs. In one small CT study, delusions were associated with basal ganglia mineralization.⁶¹ In a proton magnetic resonance spectroscopy (1H-MRS) study, delusions were associated with decreased N-acetyl-aspartate-to-creatine ratio (NAA/Cr) in the AC.⁶² In one PET study, delusions were associated with increased availability of striatal dopamine D2/D3 receptors,⁶³ which may reflect aberrant learning processes reported in schizophrenia.

In summary, neuroimaging studies of psychosis in AD are diverse. Few studies, except one,⁶³ tested a plausible causal hypothesis. Convergent studies suggest right-sided impaired perfusion and metabolism, particularly in frontal and medial temporal lobes, which dovetails with a report of psychosis associated with right-sided cerebral infarction, arguing for a laterality effect that transcends the mechanism of brain injury.⁶⁴ The relationship between psychosis and WM Δ in most but not all studies similarly suggests that control of vascular risk factors might reduce the likelihood of AD-associated psychosis.

Apathy

Apathy is defined as a reduction in motivation and initiation of activities, subdivided into cognitive, behavioral, and emotional components.⁶⁵ It is the most common noncognitive neuropsychiatric symptom of AD, present in up to 72% of patients.⁶⁶ Symptoms of loss of motivation and initiative are thought to be related to dysfunction within a network of medial prefrontal structures and fronto-subcortical networks.⁶⁷ There were two common study designs: 1) contrasting AD subjects with and without apathy and 2) correlation studies of the severity of apathy among AD subjects using dimensional apathy assessment scales (e.g., the Apathy Evaluation Scale^{68,69} or the Neuropsychiatric Inventory^{70,71}).

A few recurrent findings emerged. First, a majority of the structural neuroimaging studies reported an association between apathy and volume loss in the ACC. Those findings extended to other medial prefrontal areas and the

striatum—structures connected through cortico-striato-thalamo-cortical frontal loops.^{72–76} Second, apathy severity has been relatively consistently associated with decreased perfusion and metabolism in these areas.^{26,77–81} Third, although fewer data support a link between apathy and white matter bundles associated with these cortical structures, reduced fractional anisotropy (FA) of the cingulum bundle has been replicated.^{82–85} Multiple studies have also shown an association between apathy severity and the white matter lesion burden, particularly within the frontal lobe.¹² Reported abnormalities in temporal⁸⁶ and parietal areas⁸⁴ were not replicated across studies and modalities.

Several small studies are also of interest. One study reported that amyloid burden in MCI/AD measured with Pittsburgh B compound PET scans is higher in the frontal areas of patients with apathy, independently of atrophy measured with VBM.⁸⁷ One fMRI study reported decreased amygdalar reactivity to sad faces bilaterally in AD patients with apathy,⁸⁸ suggesting altered limbic processing of emotional stimuli. Finally, a few studies suggested that the different subcomponents of apathy (behavioral, cognitive, and emotional aspects) might have specific neuroanatomical correlates.^{76,89} For example, one SPECT study reported that 1) lack of interest was associated with reduced ACC perfusion, 2) reduced interest was associated with reduced right middle OFC perfusion, and 3) emotional blunting was associated with reduced left DLPFC perfusion.⁸⁹

Structural and functional imaging converge to support the relationship between apathy and altered function in the ACC, other medial frontal structures, and subcortical connections involving the striatum. The link between white matter lesion burden and apathy suggests that aging-related cerebrovascular change may be an important causal factor, conceivably amenable to prevention. Future studies might produce more replicable results with more precise definitions of the emotional, behavioral, and cognitive aspects of apathy to identify biologically discreet constructs.

Aggression or Agitation

The studies reported with the search terms for aggression, agitation, and hyperactivity were fewer relative to the other NCBCs.

With respect to structural studies, agitation reported in 35% of an AD sample (AD, N=31) was negatively correlated with gray-matter density in the left insula and bilateral ACC.⁷² Similarly, irritability was negatively correlated with low ACC FA and disinhibition with low ACC and fornix FA (MCI, N=21; mild AD, N=23).⁸³ These anatomical findings converge with the neuropathological observation of an association between agitation and ACC NFT density.⁹⁰

With respect to functional imaging studies at rest, lower CBF in the right medial temporal cortex (including hippocampus, parahippocampus, and amygdala, Brodmann areas 28, 35, and 36) was shown in the aggressive AD (N=30) relative to nonaggressive AD group (N=19) using Tc99mSPECT.⁹¹ Within the aggressive subgroup, aggression severity correlated

with decreased CBF in the right orbitofrontal gyrus. However, these findings were dissimilar to a smaller Tc99mSPECT study⁹² (AD with aggression, N=10; AD without aggression, N=10), in which aggression was associated with lower perfusion in the left anterior temporal cortex, bilateral dorso-frontal cortex, and right parietal cortex. An [18]FDG PET study⁶⁰ (AD, N=21) showed that agitation/disinhibition was correlated with lower global metabolism and broadly in frontal, temporal, and parietal regions.

In a task-based fMRI study to investigate affective faces in mild AD in which agitation/aggression was reported in 30% of subjects, both familiar neutral and fearful faces elicited a greater right amygdala response for AD subjects compared with elderly controls.⁹³ This group effect was most marked during the initial exposures to faces, possibly suggesting an effect of novelty. Irritability correlated with bilateral amygdala response to familiar neutral faces. Agitation also correlated with greater left amygdala response.

Although these findings are limited by lack of replication of studies, several intriguing preliminary consistent findings were demonstrated. Agitation was associated with lower volume and FA in the ACC consistent with neuropathological findings of greater NFT density. Baseline metabolism and CBF findings are less consistent: although agitation correlated with lower perfusion or metabolism broadly in frontal and temporal regions, the precise regions implicated were not consistent between studies.

Anxiety

Relative to the other NCBCs, studies of anxiety in AD were much more limited. Table S4 in the online data supplement provides a summary of the findings.

Across three structural studies, no association was observed between anxiety in AD and gray matter changes.^{42,94,95} Berlow et al.⁹⁶ showed that overall WMH volume was associated with anxiety (among other neuropsychiatric symptoms), but his methods did not allow WMH localization.

A systematic functional study by Hashimoto et al.⁹⁷ controlling for cognitive decline showed that higher anxiety correlated with lower resting metabolism in bilateral entorhinal cortex, bilateral anterior parahippocampal gyrus, and the left anterior superior temporal gyrus and left insula. After controlling for depression, delusions, hallucination, agitation, apathy, and disinhibition, the results were still significant in the right entorhinal cortex and the parahippocampal gyrus. In contrast, Sultzer et al.⁶⁰ investigated the relationship between a mixed anxiety/depression measure and rCBF showing parietal hypometabolism, a finding that contrasts with Hashimoto et al.'s⁹⁷ report of normal parietal blood flow related to both anxiety and depression.

The literature on anxiety imaging in AD patients is very limited, with no replicated studies. Anxiety may be associated with vascular white matter changes of unclear localization and possible hypometabolism in mesial temporal lobe structures.

Sleep Disorders

Regulation of arousal and sleep are mediated by a complex network that includes the brainstem, hypothalamus, thalamus, and cortex.⁹⁸ Disturbances of arousal, sleep, or circadian rhythm occur in up to 44% of patients with AD occurring early in the disorder—even predating other signs of neurodegeneration.⁹⁹ AD-related sleep disturbances include increased sleep-onset latency, decreased total sleep time, increased nighttime motor activity, decreased REM sleep, decreased slow-wave sleep, disrupted stage-2 sleep, and early morning awakening—all associated with fragmentation of sleep, often resulting in daytime drowsiness. AD is also associated with disturbances of circadian rhythm: phase delay, “sundowning,” or reversed sleep/wake pattern. Disturbances of circadian rhythm or sleep in AD are associated with diminished quality of life for both the patient and the caregiver and predict institutionalization.^{100–102} Moreover, evidence suggests that such disturbances may account for other non-cognitive behavioral problems, including wandering, restlessness, agitation, and aggression.¹⁰³

Sleep-disturbed AD patients (N=37) exhibited relatively higher CBF in the right middle frontal gyrus relative to nonsleep-disturbed AD patients (N=17) with no significant differences in perfusion from healthy controls (N=37).¹⁰⁴ Authors report that the middle frontal gyrus is implicated in REM sleep architecture regulation. Since REM onset is regulated by cholinergic inputs from brainstem nuclei, and since Eggers et al.¹⁰⁵ had reported that sleep disturbance in a case report in AD is associated with reduced acetylcholinesterase activity as measure using a cholinergic PET tracer, the authors speculated that the relative preservation of the middle frontal gyrus could be due to impaired inhibition from the thalamo-cortical ascending executive cholinergic pathways.

Together, these studies offer weak evidence for a cholinergic basis for sleep disturbance in AD. Such findings are directly relevant to understanding the biological basis of this disorder and have implications for treatment but require replication. These findings may have clinical implications suggesting that anticholinergic medications, such as diphenhydramine, may be counterproductive. Consistent with the neuroimaging findings, some evidence suggests that donepezil may improve both cognition and sleep in AD.¹⁰⁶

CONCLUSIONS

We identified dissociable neural substrates with multimodal imaging: depression implicates the lateral and superior prefrontal cortex; apathy and agitation implicate the dorsal anterior cingulate; psychosis implicates right lateralized frontal and medial temporal lobes; and anxiety implicates medial temporal regions. Frontal white matter changes appear to underlie many NCBCs, emphasizing the preventative management of vascular risk factors.

Our principal finding was that NCBCs in AD are frequently associated with vascular disease. This was reported in studies of depression, psychosis, apathy, and anxiety, but

not in agitation/aggression or sleep disturbance. The literature on agitation/aggression points to areas with higher NFT burden, while the few studies on sleep disturbance implicate the cholinergic system. The link between vascular disease and AD-related NCBC ties in to questions about the validity of AD as a unitary entity^{107,108} and whether the degree to which clinical dementia in those who meet criteria for probable AD should be attributed to A β and tau aggregates versus vascular disease.^{109,110} While the goal of this article is not to focus on nosology, we note that NCBCs seem to be associated with cerebrovascular change in many but not all studies. This ties in with a recent data-driven article demonstrating that vascular damage could be at the onset of the AD cascade.¹¹¹ We note also that the “signal” of the vascular effect might obscure relevant aspects of AD pathology that might influence the occurrence of these important behavioral disorders.

Our review also highlighted specific neural regions shown to be consistently implicated in NCBCs across several modalities. Many early studies used low resolution techniques for measuring rCBF pointing toward “frontal lobe” involvement, but more recent studies show more consistent engagement of specific well-defined regions or circuits. Highly consistent replicated findings were shown particularly for depression, apathy, and psychosis. Depression was associated with decreased perfusion and metabolism of lateral and superior prefrontal regions converging with greater frontal WMH load. Psychosis was associated with right lateralized impairments in metabolism and perfusion in frontal and mesial temporal regions with greater WMH load that was less well-localized. Different symptom presentations, such as auditory or visual hallucinations, might implicate different neural substrates associated with the relevant sensory modality. Apathy was associated with decreased volume, perfusion, metabolism, and FA in the ACC similarly converging with greater frontal WMH load. These findings extended into medial prefrontal and striatal regions, implicating fronto-striatal network impairments. Fewer studies were reported on agitation and anxiety with no replicable findings. However, agitation showed converging data across modalities, with lower volume and FA in ACC consistent with neuropathological findings of greater NFT burden in the ACC. Anxiety studies weakly suggest a possible association with impaired mesial temporal metabolism and higher WMH load.

That these findings have dissociable neural substrates has implications from a mechanistic and clinical perspective. In some cases, the metabolism or perfusion deficits appear to converge across studies with frontal WMH abnormalities suggesting underlying vascular factors. Thus, our findings suggest that vascular risk factors or imaging markers appear to be important correlates of, and are perhaps causally related to, these NCBCs, suggesting that managing underlying vascular risk factors might play a role in preventing NCBCs. The role of other aberrant neuropathological abnormalities (e.g., with NFTs in the ACC in agitation) also suggests that abnormal deposition in critical neural substrates may also be relevant to underlying impairments.

Combined with other multimodal approaches, these findings may act potentially as biomarkers for the diagnosis of specific NCBC symptoms and to track clinical outcomes. How the implicated neurocircuitry might overlap dimensionally with other behavioral symptoms in other neuropsychiatric disorders is also of great interest. Further work in larger data sets is required to assess the utility of these findings as potential biomarkers for diagnosis and optimizing therapeutic outcomes. Understanding the implicated neurocircuitry and underlying neuropathology will also allow for precision treatment targeting—for example, with noninvasive neuromodulation or pharmacological techniques—to either enhance affected circuits or optimize functioning of the remaining intact neurocircuitry.

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry, University of Southern California, Rancho Palos Verdes, Calif. (JV); the Departments of Nursing, Psychiatry, Neuroscience, and Brain and Cognitive Science, University of Rochester, Rochester, N.Y. (FVL); the Department of Psychiatry, Mercer University School of Medicine, Macon, Ga. (KLC, SDS); the University of Cambridge, Department of Psychiatry, Cambridge, United Kingdom, and Cambridgeshire and Peterborough NHS Foundation Trust (VV); and the Departments of Psychiatry, Neurology and Neurosurgery, Montreal Neurological Institute and McGill University Health Centre, McGill University, Montreal, Quebec, Canada (SD).

Send correspondence to Dr. Ducharme; e-mail: simon.ducharme@mcgill.ca

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