The Anatomical Basis of Anosognosia
(Lack of Awareness of Illness)
(updated May 2013)

SUMMARY:

Anosognosia, or lack of awareness of illness, is a common symptom of schizophrenia and bipolar disorder with psychotic features. It is one of the most common reasons why individuals with these disorders often refuse to take medication.

To date, 20 studies have been done looking at the relationship between anosognosia and the anatomical structure of the brain; 18 of the studies reported statistically significant correlations and 2 studies did not. The 2 negative studies focused on global brain measures, such as total brain or total ventricular volume. The 18 positive studies included many that focused on more specific brain structures. Two of the positive studies were of individuals with first-episode psychosis and included individuals who had never been treated with antipsychotic medications, thus ruling out medications as a cause of the observed brain changes.

Regarding localization, it is now clear that anosognosia is not caused by damage to one specific area. Rather a person’s awareness of illness involves a brain network that includes the prefrontal cortex, cingulate, superior and inferior parietal areas, and temporal cortex and the connections between these areas. Damage to any combination of these areas can produce anosognosia, but damage to the prefrontal and parietal areas together make anosognosia especially likely.

Anosognosia, or lack of awareness of illness, thus has an anatomical basis and is caused by damage to the brain by the disease process. It thus should not be confused with denial, a psychological mechanism which we all use.

INTRODUCTION:

Anosognosia has been described by neurologists for over a century. Classically, it occurs in a patient who has had a stroke in the right parietal lobe of the brain, producing left hemiplegia. The individual so affected may deny that anything is wrong despite being paralyzed on the left side. This is not simple denial, a subconscious psychological mechanism we all use.
occasionally. This is anatomical damage to the part of the brain we use to think about ourselves. Thus denial is psychological, whereas anosognosia is anatomical.

Anosognosia is very difficult to imagine or understand. Oliver Sacks, in *The Man Who Mistook His Wife for a Hat* (p.5), explained anosognosia as follows:

> It is not only difficult, it is impossible for patients with certain right-hemisphere syndromes to know their own problems – a peculiar and specific ‘anosognosia,’ as Babinski called it. And it is singularly difficult, for even the most sensitive observer, to picture the inner state, the ‘situation’ of such patients, for this is almost unimaginably remote from anything he himself has ever known.

The anatomical basis of anosognosia in stroke patients has been well described. According to a summary of the studies, anosognosia “seems to be equally frequent when the damage is continued to frontal, parietal or temporal cortical structures…[but] is highest when the lesions involve parietal and frontal structures in combination.” (Pia L, et al. The anatomy of anosognosia for hemiplegia: A meta-analysis. *Cortex.* 2004;40:367-377).

**STUDIES OF ANOSOGNOSIA IN SCHIZOPHRENIA**

Attention to the problem of anosognosia in schizophrenia is relatively new, dating to the work of Drs. Xavier Amador and Anthony David in the 1990s. Clinicians had long been aware that some patients were unaware of their symptoms and illness but the similarity of this condition to the anosognosia seen in some stroke patients had not been widely noted. Indeed, being unaware of one’s illness has been known to be a cardinal symptom of psychosis. As early as 1604, playwright Thomas Dekker had a character in his play “The Honest Whore” proclaim: “That proves you mad because you know it not.”

In the last decade there has been an outpouring of studies of anosognosia in individuals with psychosis in general and with schizophrenia in particular. Some studies have examined the relationship between anosognosia and various brain functions (for a review see Shad MU, et al. Insight and frontal cortical function in schizophrenia: A review. *Schizophrenia Research* 2006;86:54-70). Other studies have examined the relationship between anosognosia and brain anatomy in individuals with schizophrenia; this paper will summarize these studies.

There have been at least 20 such studies, beginning with the most recently published.

**20. Awareness of illness is associated with hemispheric asymmetry in schizophrenia.**

In Canada at the University of Toronto, 52 individuals with schizophrenia were assessed for awareness of illness (using the relevant item on the PANSS) and underwent MRI. Lack of awareness of illness was strongly correlated with both severity of illness (p<0.01) and with total white matter volume (p<0.01). Hemispheric asymmetry was evident with the right hemisphere having less volume than the left hemisphere in patients with impaired awareness of illness, specifically in the anterior end of the inferior temporal lobe (p=0.05); the dorsal lateral prefrontal cortex (p=0.003); and the inferior parietal lobe (angular gyrus) (p=0.05). These findings are
consistent with the occurrence of anosognosia in some individuals with strokes when the stroke occurs in the right hemisphere. It suggests that awareness of illness in schizophrenia is probably caused by damage more to the right hemisphere. Individuals with schizophrenia who retain their awareness of illness probably have less damage to these specific right hemisphere areas.

The authors of the study also noted that persons with schizophrenia vary in their degree of anosognosia: “They can have equally bizarre delusions or perceptual disturbances but can be quite dissimilar in their ability to recognize that these experiences arise from their mind rather than a part of objective reality.” This is one of the most puzzling aspects of schizophrenia for family members.


19. Awareness of illness is associated with the function of the medial prefrontal cortex, insula, and inferior parietal lobule.

In the Netherlands, 47 individuals with schizophrenia and 21 normal controls were assessed by functional MRI. They were asked to do tasks which required them to think about themselves (self-reflection) while having their brains scanned. Individuals with anosognosia (less ability to think about themselves) showed significantly poorer activation in several brain areas, including parts of the frontal and parietal lobes. These were statistical group differences but they cannot yet be used to predict anosognosia in any given individual.

The following pictures illustrate such differences. They compare two individuals with schizophrenia, one of whom has good insight (high self-reflection) and the other of whom has poor insight (low self-reflection). Figure 1 shows much better activation in the insula and the inferior parietal lobule (IPL) in the individual with good insight. Figure 2 shows much better activation in the medial prefrontal cortex (MPFC) in the individual with good insight.

Pictures courtesy of Annerieke E. de Vos, Department of Neuroscience, University Medical Center, Groningen, the Netherlands.

18. Awareness of illness is associated with the function of midline brain structures.

In Finland, 21 patients with schizophrenia and 17 normal controls underwent both structural magnetic resonance imaging (MRI) and functional MRI, during which time they were asked to answer specific questions about insight, e.g., “If someone said I had a mental illness they would
be right.” Insight was associated with activation of brain midline structure, specifically posterior cingulate, medial prefrontal cortex, and frontal pole, brain areas known to be associated with self-awareness. The authors acknowledged that “the present findings…cover only a portion of the neuronal circuitries involved in the processing of insight.”


17. Anosognosia is associated with impaired cerebral blood flow in the superior parietal area (precuneus).

In France, 31 patients with paranoid schizophrenia and 18 normal controls were assessed for cerebral blood flow by single photon emission computed tomography. 21 patients had good awareness of their illness and 10 did not. Those with poor awareness of their illness showed poor cerebral blood flow to their precuneus bilaterally (p<0.001). There were no differences in the frontal lobes. The precuneus is part of the superior parietal lobe and known to be involved in self-consciousness, including awareness of one’s own emotional state.


These pictures show differences in blood flow to the superior parietal area (precuneus) in individuals with schizophrenia with preserved awareness of illness (below) and impaired awareness of illness (anosognosia) (above).

Pictures courtesy of Dr. Eric Guedj and colleagues, Hospital de la Timone, Marseille, France.

16. Anosognosia is associated with widespread impairments in white matter.

At New York University, 36 individuals with schizophrenia and schizoaffective disorder underwent diffusion tensor imaging (DTI), which assesses brain white matter integrity. Those with poorer awareness of their illness were significantly more likely to have impaired white matter function in the frontal lobe (e.g., left middle and right superior frontal gyri); temporal lobe
(e.g., bilateral parahippocampal gyri); cingulate; thalamus; and basal ganglia (caudate and lentiform nucleus).


15. **Anosognosia is associated with decreased cortical thickness.**

In Montreal 79 individuals with first-episode psychosis were assessed clinically and by magnetic resonance imaging (MRI). Poorer awareness of illness was significantly associated with having a thinner brain cortical layer in the left middle frontal gyrus, left inferior frontal gyrus, left inferior temporal gyrus, left and right precentral gyrus, and right occipital gyrus. Impaired awareness of need for treatment was significantly associated with a thinner brain cortical layer in the left middle and medial frontal gyri; parietal precuneus and supramarginal gyrus; temporal parahippocampus and superior, middle and inferior gyri; and middle occipital gyrus. The authors concluded that “insight involves a network of brain structures, and not only the frontal lobes as previously suggested.”


14. **Anosognosia is associated with impairments in midline brain structures (posterior cingulate and precuneus).**

In England, 82 individuals with first episode psychosis and 91 normal controls were assessed on neuropsychological tests and by magnetic resonance imaging (MRI). 20 of the individuals with first episode psychosis “had no capacity to identify psychotic symptoms as pathological.” Compared with the other 62 individuals, those 20 had “significantly reduced global gray matter volume,” most marked in the left posterior cingulate cortex, the right precuneus, and the cuneus.


13. **Anosognosia is associated with impairments of impairments of temporal and parietal areas.**

In England, 52 individuals with schizophrenia or schizoaffective disorder and 30 normal controls were assessed for awareness of symptoms and underwent magnetic resonance imaging (MRI). Those with poorer awareness of their symptoms had decreased gray matter volume in their left
superior, left middle, and right inferior temporal gyri, as well as the right inferior parietal lobule and right supramarginal gyrus (all p<0.001).


12. Anosognosia is associated with decreased gray matter volume of the prefrontal cortex.

In England, 28 outpatients with stable schizophrenia were assessed for insight and underwent magnetic resonance imaging (MRI). Lower levels of insight were moderately associated with decreased volume of the prefrontal gray matter, especially the inferior frontal gyrus.


11. No association between anosognosia and regional brain volumes.

In Italy, 50 patients with schizophrenia and 30 normal controls were assessed for awareness of illness and by magnetic resonance imaging (MRI). No relationship was found between awareness of illness and the gray and white matter volumes in the frontal or temporal cortex.


10. Anosognosia is associated with decreased activation of the left medial prefrontal cortex.

In England, 14 individuals with schizophrenia were subjected to functional magnetic resonance imaging (fMRI) both during an acute schizophrenia episode and again after they had been stabilized. During their fMRI, they were asked to do tasks which measured social functioning and awareness of illness. Their left medial prefrontal cortex showed improved activation when they were stabilized, and this correlated with improvement in insight scores (r=0.81, p<0.001).

9. Anosognosia is associated with decreased volume of right dorsolateral prefrontal cortex and right orbitofrontal cortex.

At the University of Texas Southwestern, 14 patients with schizophrenia and 21 normal controls were assessed for awareness of illness and symptoms and by magnetic resonance imaging (MRI). Patients with poorer awareness of their illness and symptoms also had significantly smaller right dorsolateral prefrontal cortex (r= -0.72, p= 0.04).


8. Anosognosia is associated with reduced gray matter in the cingulate and inferior temporal regions.

In South Korea, 35 patients with paranoid schizophrenia and 35 matched normal controls underwent clinical testing and magnetic resonance imaging (MRI). Those with greater “lack of judgment and insight” had reduced gray matter in their right anterior cingulate, left posterior cingulate, and inferior temporal region on both sides.


7. Anosognosia is associated with decreased volume of the right dorsolateral prefrontal cortex.

At the University of Pittsburgh, 35 individuals with first episode schizophrenia, who had never been treated with any antipsychotic drugs, were assessed clinically, neuropsychologically, and by magnetic resonance imaging (MRI) of the frontal lobes and hippocampus. 18 patients had poor awareness of their illness and 17 had good awareness of their illness. Those with poor awareness had decreased volumes of their right dorsolateral prefrontal cortex (DLPFC) (r= -61, p = 0.008). Unawareness of illness was not associated with hippocampal volume nor with duration of illness or other clinical symptoms.


6. Anosognosia is not correlated with global brain measures.

In England, 78 men with schizophrenia and 36 normal controls were assessed for awareness of illness and underwent magnetic resonance imaging (MRI). There were “no significant
correlations between total insight score and grey, white, CSF, and total brain volume.” The authors concluded that such research was not likely to be useful for such “global brain measures” and that “future investigations should pay attention to more specific cortical regions.”


5. Anosognosia is associated with specific subregions of the frontal lobes.

At Dartmouth Medical School, 15 individuals with schizophrenia and schizoaffective disorder were assessed for awareness of illness and frontal brain structures by magnetic resonance imaging (MRI). Those with less awareness of their illness had significantly smaller bilateral middle frontal gyrus volume (r= -0.92 and -0.72, p<0.01). There was also a trend for these individuals to have a smaller right gyrus rectus and left anterior cingulate gyrus. The authors concluded that “the strong correlations between bilateral middle frontal gyri and unawareness suggest involvement of dorsolateral prefrontal cortex,” an area that has been associated with schizophrenia in many neuropsychological and neuropathological studies.


4. Anosognosia is associated with atrophy of the frontal lobes.

In Norway, 21 individuals with schizophrenia and 21 matched normal controls were assessed by computerized tomography (CT) scans. 7 of the 21 individuals with schizophrenia had mild or moderate atrophy of their frontal lobes, and this atrophy correlated with having poorer awareness of their illness (r= -0.52, p<0.05). Poorer awareness of illness also correlated with poorer executive function, a frontal lobe-associated trait, but not with other neuropsychological measures. The authors concluded that “unawareness of illness in schizophrenia may be related to frontal lobe deficit.”


3. Anosognosia is associated with having a smaller brain size.

At Dartmouth Medical School, 18 individuals with schizophrenia with a poor awareness of their illness were compared on magnetic resonance imaging (MRI) with 12 individuals with schizophrenia with a good awareness of their illness and 13 healthy controls. There were no
differences between the schizophrenia groups on education, symptoms, or severity of illness. However, those with poor awareness of their illness had significantly smaller brains and decreased intracranial volumes, findings consistent with having had a greater loss of brain tissue (atrophy) associated with their schizophrenia.


2. Anosognosia does not correlate with total ventricular volume.

In England, 128 individuals with recent-onset psychosis were assessed for awareness of illness and underwent a computerized tomography (CT) scan. No correlation was found between awareness of illness and total ventricular volume.


1. Anosognosia correlates with enlarged brain ventricles.

In Japan, 22 patients with chronic schizophrenia were assessed for awareness of illness and underwent magnetic resonance imaging (MRI). Those patients with impaired awareness of illness had significant ventricular enlargement (p<0.05).