

The Relationship between White Matter Integrity
and Self-Awareness in Multiple Sclerosis using
Diffusion Tensor Imaging

Ben Silver

Suffern High School

PERSONAL SECTION

From a very young age, I've always been incredibly interested in the brain and all that it can do. While the heart can help you circulate blood and the lungs can help you exchange oxygen, only the brain can control almost all bodily functions while simultaneously making you into the person you are. In addition, I have also always been intrigued by the idea of discovery and the fact that our understanding of life in the world is constantly changing, and the brain is the aspect of science which our understanding of is certainly changing the fastest. Although it may appear that we know an immense amount about the potentials of the mind, there is so, SO much more to learn and discover.

It is for these reasons that when I enrolled in my science research class at my school I decided to study neuroscience. After extensively reading an immense amount of journal articles, I decided to do my research at the Kessler Foundation in West Orange, NJ under the mentorship of Dr. Helen Genova. When I first got there, I was excited to jump right into creating a hypothesis and exploring it. However, because my research focused so heavily on statistics, I spent a great deal of time simply learning about the subject: different kinds of tests, different kinds of values (so many letters!), and on and on. At first, I found it a burden. Here I was, in a world-renowned research institution, with any number of resources at my fingertips, and I was sitting at a desk reading a textbook.

In the end, however, expanding my background knowledge paid off more than I ever thought it could. Because I had a true understanding of the mathematical mechanisms underlying my research, I was able to truly and fully grasp the meaning of my results. With the full background that only working in an actual lab can bring, my research wasn't just a bunch of

numbers, but rather real, tangible results with real-world applications. This was by far the most rewarding part of my research, and it is important for all people, young or old, to take the time to truly understand the meaning of their research. As many young people enter the research world, their enthusiastic minds can often take over the need for logic and common sense, as mine did. However, it is only when we can learn to combine that common sense with our enthusiasm that truly great research may come about.

INTRODUCTION

Multiple Sclerosis (MS) is an auto-immune disease that attacks the central nervous system. Almost 10,000 people are diagnosed every year, and depending on age, at least 40% of people with MS are unemployed, suggesting the severity of its debilitation within society. Specifically, it occurs when the immune system attacks the myelin sheath, a protective coating around the axons of nerve cells of the brain.^[7] The myelin sheath is composed of white matter, functioning to help nerve cells send signals quickly and smoothly throughout the brain. When it is damaged (this occurs in MS), signals cannot be sent throughout the body as quickly or efficiently. The Central Nervous System (CNS) has varied bodily functions; therefore, individuals with MS experience numerous symptoms, such as vision problems, trouble walking, and severe cognitive and physical fatigue. Such a wide range of symptoms calls for very extensive and broad treatment plans; therefore it is important to understand as many of these symptoms as possible in order to treat MS patients efficiently and effectively.

One of the more common, and noticeable, symptoms in MS is Impaired Self-Awareness (ISA).^[9] Self-Awareness is the ability to understand one's own disabilities and capabilities. People who have impaired self-awareness are unable to understand all of the problems that MS

causes them, such as reduced physical capabilities or cognitive fatigue. Although ISA has been studied extensively in MS and other neurological conditions like Traumatic Brain Injury,^[10, 18] very little is known about its neurological underpinnings. A common method of quantifying ISA is to compare scores on a questionnaire of the patient and the patient's significant other, then determine the discrepancy between the two.^[11] However, this is only a subjective result. In other words, these are purely the opinions of the patient and the patient's significant other. A more reliable form of data comes from an unbiased, objective source^[5] that is not affected by factors that normally affect subjective results. Commonly, magnetic resonance imaging has been used to obtain these kinds of objective results,^[8] but, as technology advances, Diffusion Tensor Imaging (DTI) analysis is becoming more and more commonplace as a reliable, unbiased source for objective results.

DTI is similar to an fMRI analysis, except that rather than look at grey matter activation, a DTI analysis looks at water molecule movement throughout the brain. However, this movement can most easily be seen in the white matter skeleton.^[6] White matter integrity is quantified using Fractional Anisotropy, which determines how close to "normal" water molecule movement is in white matter tracts.^[17] White matter integrity is known to be directly related to executive functioning in the brain,^[13] and it is also known that MS subjects have less white matter integrity than healthy people do.^[24] The use of DTI to examine the brain is a more recent technique than MRI; therefore less work has been done in the field. Although there have been many studies that have looked at Awareness by administering questionnaires,^[6] this is the first study to utilize an objective source such as DTI in addition to a subjective source, such as a questionnaire, to examine the relationship between the two types of results. In doing so, it will be

possible to obtain more accurate results that utilize both subjective and objective methods, in conjunction.

STATEMENT OF PURPOSE

This study seeks to examine the following: 1) Different types of self-awareness, since self-awareness can be impaired cognitively, behaviorally, and physically. 2) Since white matter integrity is related to executive functioning, and self-awareness is a type of executive functioning, this study seeks to examine if reduced white matter volume will be directly correlated with reduced self-awareness, as predicted. However, since this is an exploratory study, no particular Regions of Interest (ROI) will be examined, and the brain will be looked at as a whole.

METHODS AND MATERIALS

This section can often be confusing, so I will simplify a lot of what was done and leave out unimportant information. This study utilized data from 14 participants, all of whom were inflicted with Multiple Sclerosis. To obtain subjective results, we used the Awareness Questionnaire, which comes in two forms: a patient form, and a significant other form. The AQ also has 3 subscores: a cognitive subscore, a behavioral/affective subscore, and a motor/sensory functioning subscore. Concordance scores were used, and they were obtained by subtracting the significant other's scores from the patient's scores and taking the absolute value. For the objective measure, a Diffusion Tensor Imaging scanner calculating Fractional Anisotropy values was used. Correlations between AQ scores and FA values were run.

RESULTS

Results can also be quite confusing, and can also include a lot of unnecessary information, so I will summarize what is important. The mean AQ score was 7.43 with a standard deviation of 6.47, which are both average values for a normal MS group.

Table 2. Relationship between FA and AQ total concordance scores

	<i>Cluster Size</i>	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>t-value</i>
L Inferior Longitudinal Fasciculus	37	-41	-46	0	-3.59
L Forceps Major	36	-25	-75	15	-3.53
Uncinate Fasciculus	31	-28	-5	-11	4.30

The largest significant cluster (37 voxels) was found in the Left Inferior Longitudinal Fasciculus, while the smallest (31 voxels) was found in the Uncinate Fasciculus, as shown in Table 2. These clusters were significant in terms of FA values and AQ total concordance scores.

Correlations between FA values and each of the AQ subscores were also run, but most of what was found is unimportant in relation to the purpose and hypothesis of this study. In addition, since there were a number of significant clusters found in the AQ total concordance score correlation, subscore correlations only reinforce these results, and therefore are not entirely necessary to know about.



Figure 1. The cluster in blue indicates a negative correlation between FA values and AQ concordance scores. The cluster is situated in the Left Inferior Longitudinal Fasciculus.

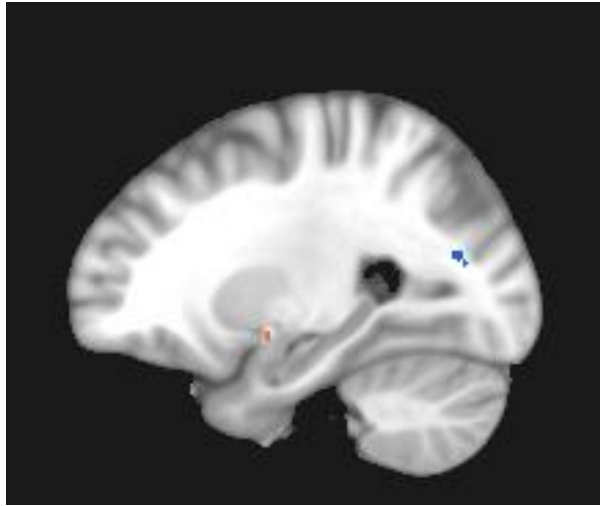


Figure 2. The cluster in blue indicates a negative correlation, while the cluster in red indicates a positive correlation. The negative correlation occurs in the Left Forceps Major while the positive one occurs in the Uncinate Fasciculus.

DISCUSSION

The aim of this study was to determine a relationship between Impaired Self-Awareness and white matter integrity in the brain. The Awareness Questionnaire (AQ) and a DTI scanner were used in order to utilize both subjective and objective results, rather than just relying on a subjective method, which is more common. It was predicted that as AQ concordance scores increased (thus indicating reduced awareness), FA values would decrease. The Awareness Questionnaire concordance scores were not significantly associated with age or time since diagnosis. One reason for this might be that although the majority of subjects had Relapsing Remitting Multiple Sclerosis, other types, such as Secondary Progressive and Primary Progressive, were also present. Different variations of MS have slightly different effects over time,^[17] so measuring time since diagnosis means different things for different subjects, and this may mask any significant results, since individual types of MS were not examined in this study. When a regression analysis was run against AQ total concordance scores in order to examine the relationship between white matter integrity and awareness, significant correlations were found in the Left Inferior Longitudinal Fasciculus, the Left Forceps Major, and the Uncinate Fasciculus.

All three of these tracts have been shown in the past to play some role in executive functioning or awareness.

The Longitudinal Fasciculus, which connects the occipital and temporal lobes, has been shown in previous studies to be related to recognition.^[19] The Superior LF has been shown to be related to object and word recognition, while the ILF has been shown to play a larger role in facial recognition. Facial recognition, and recognition in general, is certainly a type of awareness, relating to awareness of the world around the person. When looked at in terms of self-awareness, this is a behavioral type of awareness, an awareness that deals with interactions and socializations with people and objects in the world.

The Left Forceps Major is part of the splenium of the Corpus Callosum (CC). The CC connects the two hemispheres of the brain, which have very different functions. The two hemispheres communicate frequently in order to carry out more complex functions, so damage to the CC or parts of it could have very noticeable effects. Because reduced FA values were found in the splenium of the CC, it can be inferred that this part of the CC is in fact damaged, which could certainly lead to problems with executive functioning or self-awareness. In addition, in past studies, both the Forceps Major and the Forceps Minor have been shown to have ambulatory functions, specifically gait and balance.^[2] One of the subscales of the AQ was motor/sensory functioning, so finding reduced FA values in this part of the brain agrees with previous studies.

Finally, the Uncinate Fasciculus, which is a white matter tract that connects the hippocampus and amygdala, also had a significant correlation with AQ total concordance scores. The function of the UF has still not been completely explored, but it is known to play a crucial role in memory,^[14] which is a higher-functioning, cognitive aspect of the brain. In addition, the

UF has been connected to auto-noetic self-awareness,^[13] which, in addition to memory of the past, is a type of self-awareness that also includes understanding that one's memories are one's *own* memories, and that these memories make up who a person is today. Although the UF has many cognitive functions, knowing one's own experiences is in itself a type of awareness, so once again, it would be expected to find reduced FA values here in people with reduced self-awareness.

Each of three significant white matter regions have in the past been connected to areas of the brain that correspond to the three different subscales of the Awareness Questionnaire: the LILF has behavioral/affective functions, the LFM has motor/sensory functions, and the UF has cognitive functions. After this was found, further investigation was done with regression analyses to examine the relationship between FA values and AQ concordance subscales. Although the findings were not completely what was expected (For example, the Forceps Major was most closely linked with the cognitive subscale. See Tables 3, 4, and 5), it is still important to note that this study reinforces the different subscales of the AQ and agrees with previous studies concerned with the AQ.^[20]

Another important aspect of the results is the direction of the correlation. It was expected that a negative correlation would be found, which would mean as FA values went up, concordance scores went down, which means there was less discrepancy between the questionnaires and increased awareness, and for the Inferior Longitudinal Fasciculus and the Forceps Major, this is what was found. However, a few positive correlations were found in the Uncinate Fasciculus when total AQ concordance scores were used as well as every single brain region when motor/sensory functioning AQ concordance scores were used. For the brain regions in the motor/sensory functioning analysis, it is not completely clear why a correlation in the

opposite direction may have occurred. It is hypothesized that this may be related to the fact that people are more aware of their physical symptoms, as they are the most concrete, and people with MS are less impaired in terms of physical self-awareness.^[1] Another reason for the opposite correlation, which could also explain the opposite correlation in the Uncinate Fasciculus, could be related to the neural plasticity of the brain. When the brain becomes damaged or begins to degenerate, other white matter tracts strengthen and take over the functions of the damaged tracts in order to compensate. Therefore, the Uncinate Fasciculus could in fact be taking over the role of a damaged portion of the brain, leading to higher FA values related to reduced self-awareness. As brain imaging becomes more advanced, future studies could look at this effect more closely and determine if this is the reason for a correlation in the opposite direction of what was expected.

There were several limitations of this study. The first, and most important, was the patient sample. This study had a small sample of MS subjects to begin with, and many had to be excluded due to incomplete questionnaires or incomplete DTI data. This may be why no significance with AQ concordance scores related to age or time since diagnosis was found. Future studies with a larger database should explore these same questions, since places where significance was not found, but were expected to, may show a result in an expanded study. Another limitation is that there were not enough healthy controls to use for statistical analyses, so they were excluded in this study. Although the findings are still valid without a healthy control sample, it is still important that future studies analyze correlations between white matter tracts and awareness questionnaires in both MS patients and healthy controls.

Another limitation of this study has to do with the fact that although the person who filled out the significant other AQ form had a close relationship with the subject, this relationship

varied. The relationship between a husband and wife is a very different one from the relationship between a parent and their child, or the relationship between siblings. For example, a spouse may be more willing to voice the patient's inhibitions or problems, while a parent may tend to be more protective of the subject, and subconsciously rate them as having higher levels of awareness. All of these relationships were present in this study, so although the significant other was supposed to be healthy, their answers were most certainly somewhat subjective. Future studies should determine the effect, if there is one, that relationship has on a significant other questionnaire. If there is one, it could drastically change results gathered from many questionnaires with a significant other portion.

Finally, another limitation is that although age of the *subjects* was controlled for when running DTI analyses and t-tests, age of the significant others was not known and therefore *not* controlled for. The significant others were "healthy," but depending on their age, they themselves could have had varying degrees of awareness about themselves and people close to them.^[10] All of these reasons could mask significant results in AQ concordance scores when compared to age or time since diagnosis, and once again show that there are numerous problems with relying on subjective results and an objective source to use as a comparison is strongly needed.

CONCLUSION

The aim of this study was to examine the relationship between Fractional Anisotropy values (using DTI) and Awareness Questionnaire concordance scores. These tools were used in order to obtain both subjective and objective results, and show the need for both of them, rather relying on one. It was predicted that as FA values decreased (a decrease in white matter

integrity), self-awareness would also decrease. When looking at the AQ alone, no significance was found in relation to age or time since diagnosis. When a regression analysis was run between AQ and FA values, significant correlations were found in the Left Inferior Longitudinal Fasciculus, the Left Forceps Major, and the Uncinate Fasciculus.

Future research should use a much larger sample size that includes healthy controls. The reasons why no significant correlations were found when comparing the AQ to certain descriptive statistics should certainly be explored, along with reasons for positive correlations when comparing FA values and AQ concordance scores. Finally, significant white matter tracts and their functions should be examined even further in order to expand the knowledge of the brain and its capabilities.

REFERENCES

1. Abreu, Beatriz, , et al. "Levels of self-awareness after acute brain injury: How patients' and rehabilitation specialists' perceptions compare ." *Physical Medicine and Rehabilitation*. 82.1 (2001): 49-56. Web. 21 Aug. 2012.
2. Bhadelia, Refeeque. "Diffusion Tensor Imaging, White Matter Lesions, the Corpus Callosum, and Gait in the Elderly." *Stroke*. 40. (2009): 3816-3820. Web. 21 Aug. 2012.
3. Baudewig, J., Dechent, P., Merboldt, K. D., & Frahm, J. (2003). Thresholding in correlation analyses of magnetic resonance functional neuroimaging. *Magnetic Resonance Imaging*, 21(10), 1121-1130.
4. Chiaravolloti, Nancy, , et al. "Increased cerebral activation after behavioral treatment for memory deficits in MS." *Journal of Neurology*. 259.7 (2012): 1337-46. Print.

5. DeLuca, John, , et al. "Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI." *Journal of the Neurological Sciences*. 270. (2008): 28-39. Print.
6. Evans, C. C., , et al. "Early impaired self-awareness, depression, and subjective well-being following traumatic brain injury." *Journal of Head Trauma Rehabilitation*. 20.6 (2005): 488-500. Web. 20 Aug. 2012
7. Frohman, E. M., M. K. Racke, and C. S. Raine. "Multiple sclerosis — the plaque and its pathogenesis." *New England Journal of Medicine*. 354. (2006): 942-955. Web. 20 Aug. 2012.
8. Giacomini, Paul, and Douglas Arnold. "Non-conventional MRI techniques for measuring neuroprotection, repair, and plasticity in multiple sclerosis." *Current Opinion in Neurology*. 21. (2008): 272-277. Web. 20 Aug. 2012.
9. Goverover, Yael, , et al. "The relation between subjective and objective measures of everyday life activities in persons with multiple sclerosis." *Arch Phys Rehabil*. 86. (2005): n. page. Print.
10. Goverover, Yael, , et al. "The relationship between self-awareness of neurobehavioral symptoms, cognitive functioning, and emotional symptoms in multiple sclerosis ." *Multiple Sclerosis Journal*. 11.2 (2005): 203-212. Web. 20 Aug. 2012.
11. Goverover, Yael. "The Relationship Among Performance of Instrumental Activities of Daily Living, Self-Report of Quality of Life, and Self-Awareness of Functional Status in Individuals with MS." *Rehabilitation Psychology*. (2009): n. page. Print
12. Java, Rosalind. "Effects of age on state of awareness following implicit and explicit word-association tasks." *Psychology and Aging*. 11.1 (1996): 108-111. Web. 21 Aug. 2012.
13. Levine, B., , et al. "Episodic memory and the self in a case of isolated retrograde amnesia." *Brain*. 121. (1998): 1951-1973. Web. 20 Aug. 2012.
14. Mabbot, DJ. "The relations between white matter and declarative memory in older children and adolescents." *Brain Research*. 1294. (2009): 80-90. Web. 21 Aug. 2012.
15. Murray, TJ. "Diagnosis and treatment of multiple sclerosis." *British Medical Journal*. 332.7540 (2006): 525-527. Web. 21 Aug. 2012.
16. Nebes, R.D., Meltzer, C.C., Whyte, E.M., Scanlon, J.M., Halligan, E.M., Saxton, J.A., et al. (2006). The relation of white matter hyperintensities to cognitive performance in the normal old: education matters. *Neuropsychology, Development, Cognition. Section B Aging, Neuropsychology Cognition*, 13, 326-40.
17. O'Donnel, Lauren, , et al. "An introduction to diffusion tensor image analysis." *Neurosurgery Clinics of North America*. 22.2 (2011): 185-193. Web. 22 Aug. 2012.

18. O'Keefe, Fiadhnaid, , et al. "Awareness of deficits in Traumatic Brain Injury: A multidimensional approach to assessing metacognitive knowledge and online-awareness." *Journal of the International Neuropsychological Society*. 13. (2007): 38-49. Web. 20 Aug. 2012.
19. Orbitus, Els, , et al. "Integrity of the inferior longitudinal fasciculus and impaired object recognition in children: a diffusion tensor imaging study." *Developmental Medicine and Child Neurology*. (2011): 38-43. Web. 21 Aug. 2012.
20. Sherer, M., Bergloff, P., Boake, C., High, W., & Levin, E. (1998a). The Awareness Questionnaire: Factor structure and internal consistency. *Brain Injury*, 12, 63-68.
21. Sherer, Mark, , et al. "Early impaired self-awareness after traumatic brain injury." *Physical Medicine and rehabilitation*. 84.2 (2003): 168-176. Web. 20 Aug. 2012.
22. Sherer, M. (2004). The Awareness Questionnaire. *The Center for Outcome Measurement in Brain Injury*. <http://www.tbims.org/combi/aq>
23. Smith, Stephen, , et al. "Tract-basedspatial statistics: Voxelwiseanalysisof multi-subject diffusion data." *Neuroimage*. (2006): n. page. Print.
24. Van Hecke, W, , et al. "Correlation of cognitive dysfunction and diffusion tensor MRI measures in patients with mild and moderate multiple sclerosis." *Journal of Magnetic Resonance Imaging*. 31.6 (2010): 1492-8. Web. 20 Aug. 2012.