Meet Edith Sullivan, Ph.D.

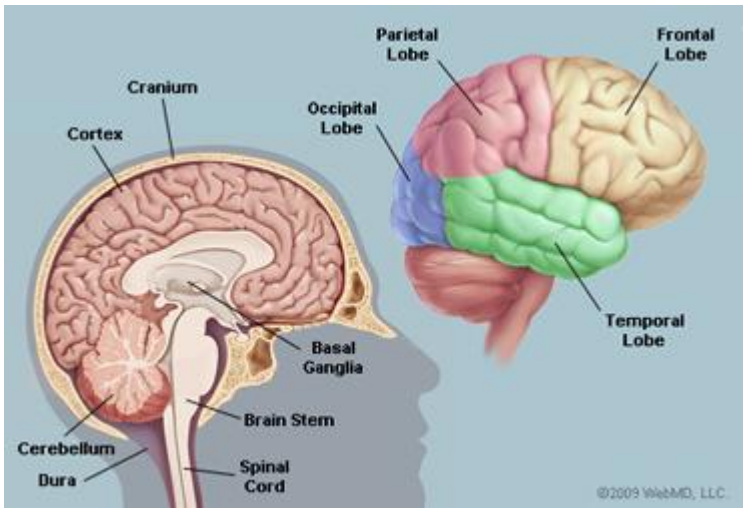
Writer Sherry Wasilow interviewed Dr. Sullivan from her office in the Stanford Institute for Neuro-Innovation & Translational Neurosciences at the Stanford School of Medicine.

SW: Do you approach your research with any particular goal in mind?

"When I was with my daughter-in-law in a hospital prenatal care suite, a medical student took her history and, to his credit, asked her how much she drank," said Sullivan. "After the interview, I asked him what he would do with such information if she had said she had drunk a large amount. Unfortunately, he had no answer. We need to educate the profession not only to ask about hazardous alcohol use, but why it is important to ask, and then what to do about it."

SW: How did you evolve from your early studies on amnesia to your current focus on alcohol dependence?

ES: Before studying alcoholism and alcoholism-related memory disorders, while I was a researcher at Massachusetts Institute of Technology (MIT), I had the privilege of testing the amnesic patient, H.M., who was not alcoholic but had intractable epilepsy and had undergone surgery to remove brain tissue that was believed to be causing the virtually daily, life-threatening seizures he suffered. The surgery performed to treat his seizures removed an extensive amount of brain tissue in the medial temporal lobes, including nearly all of the hippocampal tissue in both hemispheres of his brain. In addition to reducing the frequency and severity of H.M.'s seizures, this surgery caused his profound memory impairment. Great controversy arose at that time regarding the brain structure that causes of amnesia noted patients with bilateral medial temporal lobe lesions, like H.M. (although his amnesia was perhaps the most dense recognized), compared with amnesia characteristic of patients with diencephalic and thalamic lesions (thought not to have severe hippocampal damage), like those presumed in alcohol-related Korsakoff Syndrome (KS). This early controversy pre-dated high-resolution brain imaging.



In struggling to resolve the controversy, at least within my own conceptualization of amnesia, I became aware of impairments in cognitive and motor functions that non-amnesic alcoholics commonly endure. Placing KS amnesia in the context of additional non-mnemonic (non-memory) impairments served to complicate the KS amnesia picture, which from my perspective needed further exploration.

SW: What is Korsakoff Syndrome?

ES: Korsakoff Syndrome is a neurological disorder characterized by disproportionate memory loss in relation to other cognitive abilities. It is thought to result from a deficiency of thiamine (vitamin B1). In the United States, most cases occur in individuals who abuse alcohol.

Alcoholic KS was one of the primary causes of global amnesia, and these patients helped memory theorists recognize that memory is not a unitary function but is composed of multiple component processes. Some of these processes – most characteristically, those that enable us to remember specific events and new information – are devastated in classical amnesic disorders such as KS and Alzheimer's disease. Yet some other memory processes remain relatively unaffected, such as those involving motor procedural learning (such as riding a bicycle) and visual and verbal priming (such as being unwittingly biased by preceding information that modifies a response).

SW: What came next?

At that time in my career, I was fortunate to become a member of the brain imaging and electrophysiology laboratory of Adolf Pfefferbaum, M.D. in California. Dolf had--and still does have-- an active and highly respected program of research in alcoholism, was publishing seminal work in alcoholism, and had embarked on studies of structural brain imaging using methods for image quantification he had developed. This meant I could use brain imaging to complement my neuropsychology research. Furthermore, Dolf's laboratory had an active alcoholism research program that was working with individuals with alcohol-use disorders (AUDs) and KS from the local Veterans Affairs.

This meant I could pose questions about selective cognitive and motor functions that were spared or impaired in chronic alcoholism, whether or not they were complicated by KS, and at the same time use brain imaging to quantify tissue in brain regions at the center of the memory controversy. Although not all has been resolved, we have discovered through neuroimaging one piece of the puzzle: despite earlier beliefs, KS patients do have hippocampal atrophy, the extent of which correlated with the severity of their amnesia. Thus, we found quantitative evidence that the so-called diencephalic amnesia also had a medial temporal lobe (i.e., hippocampal) source.

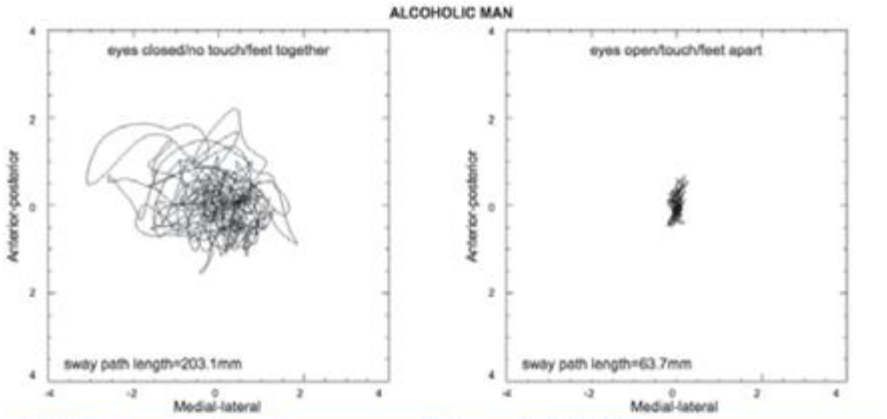
SW: Describe your current research activities.

As my years of alcoholism research have evolved, I have become especially interested in nonamnesic alcoholism and the subtler cognitive and motor impairments such individuals sustain. Cognitive functions that are commonly affected in persons in recovery from alcoholism are *working memory* (especially for nonverbal material, like spatial locations and directions), *visuospatial abilities* (such as following directions on a map or assembling pieces to make something like a piece of furniture), *problem solving*, and *conflict resolution*.

One finding that surprised me when comparing level of impairment across domains of cognitive functions was the profound problem that even persons in long-term recovery from alcoholism exhibited in their ability to stand still. *We found that, on average, the deficit in quiet standing was substantially greater than the*

significant deficits observed in cognitive functions. In our longitudinal studies, we have found this balance may improve, that improvement is correlated with signs of improvement in brain structure (notably, ventricular shrinkage), and that the time to recovery is longer in alcoholic women than men.

Our research often uses a force platform, capable of recording tiny movements in subtle sway made while trying to stand still. Sometimes during quiet standing, study participants are permitted to use stabilizing factors, such as keeping their eyes open, touching a non-weight-bearing post rather than keeping arms at their side, or standing with feet apart rather than with feet together. We have found that without the advantage of visual, tactile, or stance aids, individuals with AUDs wobble significantly more than healthy individuals on the force platform. With cues, however, individuals with AUDs are able to quell their sway almost to the level of healthy persons. The points I wish to note here are that 1) individuals with AUDs are still at a heightened risk of falling even long into sobriety, and should be warned of this risk; and 2) problems with balance can be reduced with simple aids from touch, vision, and stance.



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Sullivan, E.V., Rose, J., & Pfefferbaum, A. (2009). Mechanisms of Postural Control in Alcoholic Men and Women: Biomechanical Analysis of Musculoskeletal Coordination During Quiet Standing. *Alcoholism: Clinical & Experimental Research*, 34(3), 528-537.

We combined these studies of postural stability with examining the brain structures of both the individuals with AUDs and the group of healthy individuals used as the study control group. We found that the longer sway paths of those people suffering from alcoholism correlated with the size of their cerebellar vermis, a structure in the back of the brain known to be important for gait and balance and affected by chronic alcoholism. This led us to the next step: maybe the cerebellar vermis – traditionally considered supportive of motor control only, but recently gaining support as a cognitive control center as well – contributes to the cognitive impairment signature of alcoholism. This is our current research focus, with a focus on brain circuitry.

SW: What direction do you anticipate your research will take?

Our functional magnetic resonance imaging (fMRI) studies indicate that certain cognitive and motor functions require activity of neural systems that far-reaching across the brain. In particular, these fMRI studies have revealed that individuals with alcoholism can at times perform certain cognitive tasks as well as nonalcoholic individuals, but to do so may need to recruit different brain systems from nonalcoholic men and women to accomplish a test task at normal levels.
Furthermore, by using diffusion tensor imaging – a neuroimaging method that can provide information about the microstructure and quality of tissue, especially white matter tracts that connect far-reaching structures

of the brain – we have found that white matter fiber tracts can be affected by alcoholism. However, there is the possibility that white matter degradation can undergo repair. Perhaps some of the functional recovery we see in alcoholics who remain sober over prolonged periods may be attributable to repair of white matter microstructure.

SW: What are the day-to-day applications of your research?

There are several facts I strongly believe that therapists, families of persons suffering from alcoholism, and society at large should appreciate:

- One, even mild impairments can hamper everyday functioning and rehabilitation efforts.
- Two, alcohol dependence changes the brain and those brain changes can themselves help maintain dependency.
- Three, neurological recovery takes time, from months to years.

There are both dangerous and mild impairments. The dangerous ones include postural instability while standing; these can be especially troublesome in the dark and without stabilizing factors, such a stable surface to touch while walking. Yet, even though mild impairments such as cognitive and motor problems are subtle and require specialized testing to detect, they are clinically relevant because they reduce capacity for multi-tasking.

Families and individuals with AUDs both are often unaware of the severity of the drinking problem. Everyone should know about the 1-2 drinks a day limit, with a day-a-week holiday; that is, no more than 1 drink a day for women, and 2 drinks a day for men, and everyone needs a day a week off from drinking.

SW: What would you like to see happen in the addiction-research field?

We should know more about the beneficial effects of alcohol and who can benefit and who remains at risk for further harm. What are the scope and limits of brain-function recovery? What neurological and neuropsychological functions recover and which ones remain impaired or sub-standard? What is the course of recovery and what are the neural mechanisms of recovery?