84| Behavioral Variant Frontotemporal Dementia – With Dr. Bruce Miller

December 1, 2021

NAVIGATING NEUROPSYCHOLOGY

This is an audio transcription of an episode on the Navigating Neuropsychology podcast. Visit www.NavNeuro.com for the show notes or to listen to the audio. It is also available on the following platforms:

Listen on Apple Podcasts | Listen on Google Podcasts | LISTEN ON STITCHER | Listen on Spotify

Speakers: Bruce Miller, John Bellone, Ryan Van Patten

Intro Music 00:00

John Bellone 00:17

Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior, brought to you by INS. I'm John Bellone...

Ryan Van Patten 00:26

...and I'm Ryan Van Patten. Today we speak with Dr. Bruce Miller about behavioral variant frontotemporal dementia or bvFTD. Bruce is a behavioral neurologist at the UCSF Memory and Aging Center and is world renowned for his work in FTD and in dementia more broadly. He has been featured on 60 Minutes, the New York Times, documentaries such as Robin's Wish, and other outlets.

John Bellone 00:55

Behavioral variant FTD is the most common of the three FTD variants, with the other two being primary progressive aphasia and motor variant FTD. It's also important to distinguish between frontotemporal dementia, a clinical syndrome, and frontotemporal lobar degeneration, or FTLD, which refers to the neuropathology of the disease.

Ryan Van Patten 01:19

Much more information on bvFTD is coming up in this episode. The beginning of our conversation with Bruce is pretty heavy on genetics, neuropathology, and neuroimaging. It's great information, but it can be a bit dense for some listeners. For those of you who want to hear more about the behavioral and cognitive aspects of bvFTD, we start moving into those topics around 35 to 40 minutes* into the conversation. And, with that, we give you our conversation with Bruce Miller.

Transcriber's note: At 42 minutes.

Transition Music 01:51

John Bellone 02:01

Okay, Dr. Bruce Miller, welcome to NavNeuro. Really excited to have you.

Bruce Miller 02:04

Great to be here, John, with you and Ryan. Thank you for having me.

John Bellone 02:09

Why don't we start off by talking about, in the broadest and simplest sense, how you conceptualize and explain [the] relationships between behavioral variant FTD, language variant FTD, so-called primary progressive aphasia, the so-called

Parkinson's plus syndromes, ALS. There are lots of overlapping symptomatology here.

Bruce Miller 02:34
Great. I mean, at one time, there was one name that subsumed all of these entities and that was Pick's disease. Pick's disease was a term that captured degenerative diseases of the frontal and anterior temporal lobes. At the same time, it also captured some diseases that we now call corticobasal degeneration, progressive supranuclear palsy, that are part of the FTD spectrum. So around 1998, a group of us led by David Neary met in Ontario to develop research criteria for frontotemporal dementia, which at that time was one syndrome. And the meeting was very exciting. We ended up separating frontotemporal dementia into three groups. One was behavioral variant frontotemporal dementia. The other we called semantic dementia. The third was progressive nonfluent aphasia. We didn't have a lot of reason to separate these entities at that point, at least not from a molecular point of view, but the separation in many ways proved prescient.

Bill Seeley wrote a really nice paper in Neuron in 2007 where he looked at these three entities, and then did a quantitative measurement of the brain in behavioral variant FTD. These individuals had bifrontal insular atrophy. The patients with semantic dementia, we now call it semantic variant of PPA, had bitemporal atrophy. Then the third group, the nonfluent aphasias, had left frontoinsular atrophy. In this paper, Bill showed that these are three different regions that represent circuitry that is affected in frontotemporal dementia spectrum disorders.

Over time, we've learned that this anatomic specificity also has some molecular specificity. Amazingly, and this is why neurology and neuropsychology are so fascinating, the nonfluent aphasia, which hits the left frontal insular region, in 85% of the time is associated with tau aggregates. An anatomic specificity then leads you to a molecular specificity - quite an amazing discovery. Even more amazing, most of the other cases that are not tau related carry a mutation in the progranulin gene. This is the biggest leap that we have had in nomenclature and diagnosis. If you have a nonfluent aphasia and you do not have a progranulin mutation, you almost certainly have tau as the cause. Conversely, and this, again, is neuronal specificity at its most fascinating, if you have the semantic variant, which has bitemporal atrophy, the likelihood is about 85% that you have a certain type of aggregation of the molecule TDP-43. This is rarely genetic. [It's] usually TDP-43, a smattering of cases with tau pathology. Then, finally, the behavioral variant turns out to be much more heterogeneous. About 60% of those behavioral variants are TDP-43, 40% are tau. And then even more precision, many of TDP-43 patients

have a certain type of aggregation of the TDP molecule that is called TDP-B. Almost all of those people, if they have not already manifested ALS, are on their way to ALS. Three anatomies, three different syndromes, all with their own neuropsychology, and three different patterns of molecular degeneration.

Ryan Van Patten 07:41

In today's conversation we'll be focusing on behavioral variant FTD. Just so our listeners know, FTD can refer to a language variant as well, in terms of nomenclature. John and I will use FTD in this conversation to mean behavioral variant FTD.

So, Bruce, if you don't mind, briefly describe and summarize the 2011 Rascovsky International Consensus Diagnostic Criteria for FTD.

Bruce Miller 08:09

We set out in 2011 to refine the diagnostic criteria for the progressive aphasias, that effort was led by Marilu Gorno Tempini, and then also the behavioral variant. Based on much of the data that we had collected in our NIH-funded program project grant, we decided that, for the clinical syndrome, there were six major features: disinhibition, apathy, overeating, repetitive compulsive behaviors, loss of empathy or sympathy, and then executive loss with sparing of visual spatial function. To meet possible criteria, international criteria, you needed three of the first six items. And then to meet probable [criteria], we added that you had to show frontotemporal atrophy on an image or hypometabolism on a PET scan, or the presence of a known mutation for FTD. Even today, almost all of the research studies for bvFTD, all of the clinical trials that are starting to emerge, use these criteria and they require probable bvFTD. I should also comment that these are remarkable clinical criteria because they emphasize for a well-established neurodegenerative disease that almost all the symptomatology is psychiatric. We've never had a disease entity in neurology where the criteria were all behavioral. And by the same token, in psychiatry, they have never had research criteria for an entity for which they knew the underlying circuitry. It is a remarkable advance in the field of neuropsychiatry.

John Bellone 10:21

It also makes it difficult sometimes to distinguish it from some psychiatric conditions, which we'll talk about a little bit later.

Bruce Miller 10:30

That is the one of the reasons that we insisted, for clinical trials, that you had to meet probable criteria. With the probable criteria, you had either a mutation or atrophy in the front part of the brain, more than we see in traditional psychiatric disorders.

John Bellone 10:51

I know you had talked at the beginning a little bit about TDP-43 and tau pathology. I was wondering if you wanted to say anything about fused in sarcoma protein pathology or more about the Pick bodies and cells in regards to their prevalence in bvFTD.

Bruce Miller 11:09

We have two types of molecular pathology. One is tau. And in the case of tau, we know from mutations in the tau gene, which were discovered by Michael Houghton in 1998, that misfolding of the tau protein or abnormal aggregation of the tau protein in the frontotemporal basal ganglia regions is associated with either a progressive aphasia or with a bvFTD syndrome. This brought the discovery of the tau mutation into the front and center of discussions in dementia around molecular pathology. In modern times, in 2021, what we start to think about is, "Well, if misfolding of that tau protein and abnormal aggregation causes neurodegeneration, can we figure out a way to tell the cell to increase the degradation of that bad tau protein or prevent its production?" I think we'll touch on that a little bit later when we talk about treatment.

With the TDP-43, it's a very different mechanism. With TDP-43, what we think happens is that this protein, which is critical for the regulation of gene expression, leaves the nucleus. The function of that TDP-43 protein is no longer present. Don Cleveland at San Diego has shown that there are about 100 proteins that are dysregulated when TDP-43 leaves the nucleus. Some proteins are increased in their production, others decreased. Don believes that the stathmin protein, which is downregulated when TDP-43 leaves the nucleus, is critical for the FTD syndrome associated with TDP. The fused in sarcoma protein, FUS, which accounts for about 10% of bvFTD, works in a very similar way that TDP-43 does. The FUS protein leaves the nucleus, its regulation of gene expression is altered, and you develop a degenerative disease.

FUS is a very interesting subtype because these individuals almost always present with a bvFTD syndrome. Many of them are under the age of 40, and we have seen people in their 20s. Despite the presence of massive atrophy in the caudate

nucleus, these people have no changes in movement and they develop psychosis and profound behavioral alteration. You can imagine a lot of these individuals are misdiagnosed as having schizophrenia or bipolar illness.

Ryan Van Patten 14:33

I'm wondering if we can compare the FTD or FTLD state of the literature to Alzheimer's disease for a moment. Where, in AD, researchers have grappled with this so-called amyloid hypothesis and a controversy around whether amyloid is the upstream cause of AD or simply a downstream marker. What do we know about the ultimate cause and then the later temporal progression of FTLD and bvFTD?

Bruce Miller 15:01

We have really direct evidence with FTD that if you have a genetic mutation in tau you will get frontotemporal dementia. This really tells you that misfolding of tau is causal in a subtype of FTD. By the same token, with TDP-43, we don't necessarily think that the TDP-43 alone is responsible for the disease. But we think it's loss of function, it's movement from the nucleus into the cytoplasm, that starts a cascade of abnormal protein expression that is responsible for the illness. Now, the interesting idea about this is that some people, Don Cleveland in particular, have hypothesized that if we upregulate one of those proteins that TDP regulates, stathmin, that we can prevent the neurodegenerative process. In some ways, at least for the molecular subtypes of frontotemporal lobar degeneration, the pathologic entities that we're talking about show real promise in terms of developing molecular therapies. We know what happens, we know the cause. We know it better in some ways than Alzheimer's disease, which has been more extensively studied.

John Bellone 16:37

FTD is more heritable than some other neurodegenerative conditions. I've seen 25 to 40% in some studies. Can you summarize what we know about the genetics of bvFTD, both the familial and also the sporadic types? And the deterministic as well as risk genes.

Bruce Miller 16:55

So, traditionally, there are three major proteins that account for over 50% of frontotemporal lobar degeneration. The first is tau, which I've talked about. We have a number of mutations in the tau protein that if you develop this, you will develop with high certainty, almost 100% certainty, frontotemporal dementia clinically, frontotemporal lobar degeneration pathologically.

The second mutation that was discovered, and this was Rosa Rademaker and her team at Mayo, and also Christina Van Broeckhovenin in Poland, they discovered that a mutation in the progranulin gene causes another subgroup of genetic forms of FTD. The progranulin mutation is a little different than the tau in two major ways. The first is that it isn't completely dominant. If you are part of a family that carries this mutation, some of you - we think about 10% by the time you're 70 - have still not expressed FTD. Over 80, we have had people who have not yet developed FTD. About 10% of people over the age of 70, even though they carry this very malignant mutation, never get sick with the disease. Mechanistically, progranulin is very different than tau. We think this is a deficiency syndrome. When you don't produce enough progranulin, this triggers a pathologic cascade that leads to neurodegeneration usually in the frontotemporal region. I should add it's also a risk factor for Alzheimer's and Lewy body pathology. Progranulin, we think the future, and we'll touch on this, will be replacing this missing protein associated with a mutation.

The third mutation, which is far and away, at least I think in northern Europe and in the United States, the major mutation, is C9ORF72. This mutation is the major cause for frontotemporal dementia of the genetic type and also the major cause for ALS of the genetic type. This is a big mutation, very important. The families are fascinating. I've been following families since the 1980s who I now know carry this mutation. And in these families, some people develop an FTD syndrome, other people develop an ALS syndrome, and some people develop both at the same time. Why one person with a mutation gets ALS and another FTD remains the big mystery. The mechanism for this mutation is more like Huntington's disease. We have a large, abnormal repeat in the chromosome, and this C9ORF72 repeat is very toxic to the cell. Again, when we start to think about therapies for this, we think if we could delete the abnormal repeat that we might really have a cure for the disease.

Then there are a smattering of other cases that are associated with FUS mutations, TDP-43 mutations, often these cases have ALS along with the FTD. And then recently, we have learned that there are a number of mutations and genes associated with regulation of lysosome. Jen Yokoyama at UCSF has shown that polymorphism in the MFSD8 gene can cause frontotemporal dementia as well. This is a heterogeneous genetics. What holds it all together is the susceptibility to degeneration in the frontotemporal region. So fascinating, again, in terms of the mystery of neuronal specificity. But we're now moving from that broad idea all the way down to the molecular basis for this.

John Bellone 21:34

Do we have a sense in terms of the percentage of sporadic versus these more familial, deterministic presentations?

Bruce Miller 21:43

It's a great question. Nobody's written the definitive paper on this question. I think maybe when we really develop precision medicine for this, and we really understand all of the polymorphisms and mutations, that approximately 30% of FTD will be autosomal dominant in some way or shape or form. Maybe 70% will be sporadic. But in those sporadic cases, just like Alzheimer's disease, there will almost certainly be genetic polymorphisms that we can carry in our genome that increase our susceptibility to neurodegeneration. But that definitive paper I have not seen yet.

John Bellone 22:31

Generally speaking, can you tell us about the current state of the literature on fluid biomarkers for diagnosing bvFTD?

Bruce Miller 22:40

Another important question. For clinical trials, clearly, we want some sort of genetic analysis and determination of whether or not people have any of the mutations that I've talked about. That's important. The other big breakthrough that we've had in fluid biomarkers is the neurofilament protein. We've learned in the genetic forms, particularly C9ORF72 and progranulin, that when someone is on the verge of developing the FTD clinical syndrome, maybe they have mild behavioral problems at this point, the NFL starts to rise. We think this is going to be a great biomarker for clinical trials. Because if you can intervene when the neurofilament is starting to rise, perhaps even before someone has any clinical deficits, this might be a really powerful intervention. NFL is the big one right now. I think there will be others, but this is the one I'm particularly excited about.

Ryan Van Patten 23:58

Relatedly, and you've touched on this, but will you describe the most common patterns seen on neuroimaging for bvFTD? Structural MRI, FDG-PET and SPECT in particular for clinicians?

Bruce Miller 24:12

When I left UCLA in 1998, I believe that most of the gold in diagnosis was with PET or SPECT. I changed my mind a little bit when I came to UCSF and did a

head-to-head comparison of the two. I've discovered that most of what we saw with PET and SPECT we could also see if we were cautious and really precise. We could see that same hypometabolism that we saw with glucose or hypoperfusion with SPECT with atrophy as well. The atrophy patterns are something that are really important for clinicians. Don't necessarily expect your radiologist to comment on this. You have to learn yourself how to quantify atrophy when you get images from patients. The general theme is frontotemporal atrophy. Big involvement of the insula, which is an area that neurologists, psychiatrists, psychologists have not really thought a lot about but it's a critical area in bvFTD in particular. If it is more left sided, well, expect a language syndrome. If it is more temporal, it is usually a semantic variant of the progressive aphasia. If it's more left frontoinsular, then expect that you're going to have nonfluent aphasia. As I mentioned before, these patterns are really important because they predict molecules as well.

Ryan Van Patten 25:57
The MRI atrophy and a PET hypometabolism tend to match. Right?

Bruce Miller 26:03
They're very close.

Ryan Van Patten 26:04
Yeah.

Bruce Miller 26:05

My friend and partner in research Gil Rabinovici, who is, I think, one of the world's experts in PET, disagrees with me a little bit. He thinks that, at least in some cases, the PET abnormalities precede the atrophy. But I think he would also agree that the two are very close.

John Bellone 26:26

It's funny that you said that comment about the radiologists because I was going to ask if they usually have an eye for it. Sometimes, as a clinician, I just have the radiologist's summary and they say "global atrophy" and I don't know what to make of that. Do you have to really have an eye for that differential?

Bruce Miller 26:44
This may be changing. Our radiologists at UCSF now are tuned into this. We did a paper about 10 years ago, Jomar Suarez from Puerto Rico was the first author, and

Jomar showed that in, I think, 44 patients that we diagnosed with bvFTD based on the image and the clinical syndrome, only four of them had the radiologist commented on the specificity of the atrophy. I think [for] most of those four we had asked the question, "Is this frontotemporal dementia?" So, traditionally, radiologists - it's not that they don't see this, but they have not been trained to report it. It's just not been part of the way they think about images. I hope this is changing, but I still think if you're going to do this right, whether you're a neuropsychologist, psychiatrist, or neurologist, you've got to look at the image yourself.

John Bellone 27:49

So for a neuropsychologist who maybe isn't trained in seeing this neurodegeneration on an MRI, would it be advisable to recommend FDG-PET or SPECT or some other type of imaging to be confirmatory?

Bruce Miller 28:06

Well, I would put it this way: I think modern training in neuropsychology and psychiatry will include anatomic training around the structural basis of behavior. I think in the next decade neuropsychologists will be very comfortable looking at structural and functional scans. We have really emphasized this in our own training programs. Our neuropsychologists, in our clinical cases, I always ask them to comment on the atrophy. It's not rocket science, either. I teach our research coordinators to see this and comment on it and these are people who just have finished college. I think this is something that will evolve. Radiologists will get better at calling it. Neuropsychologists, psychiatrists, and neurologists will also be more and more comfortable with seeing these patterns. Usually they're gross, really gross. By the time someone comes into our research program, they usually have five or all six of the possible criteria, a florid clinical syndrome and pretty massive atrophy that is highly visible.

Ryan Van Patten 29:34

Speaking of gross patterns in bvFTD, atrophy tends to be more right than left. Will you talk about the reliability of this finding and what it tells us about the disease syndrome?

Bruce Miller 29:47

In this Neuron paper that Bill Seeley wrote, we found right more than left. Phenotypes are a little bit idiosyncratic - we're all wired a little differently. But almost all of us are wired so if the atrophy is predominantly left, you end up with a progressive aphasia. If it's predominantly right, there isn't much language and

there's mostly behavior. But I've learned since we reported this, a lot of people see left more than right in their cases. The key is bifrontal. When it's bifrontal temporal, behavior tends to predominate. I will also add that there are some patients, we saw one in my clinic a week ago, where sometimes it's a little hard to say what is predominating: behavior or language. We had a gentleman who had progressive reduction of speech, which is common with nonfluent aphasia, but also a behavioral syndrome that was subtle. We eventually decided that he was a bvFTD. His imaging showed left frontoinsular more than right. That's why it was a little difficult to place him into one, language, or two, behavior. There's a lot of variability.

Ryan Van Patten 31:22

This foundation of imaging, neuroanatomy, neuropathology you've been talking about is great, very helpful to ground us. We are going to start moving into behavior and personality now in a few minutes. Before we go into that too much, can you tell us a bit about the FTD phenocopy syndrome?

Bruce Miller 31:41

One of the most fascinating syndromes, I think, that we have ever faced in the study of FTD. John Hodges, my friend in Cambridge, England, with Chris Kipps, put together a really elegant paper where they talked about patients that they had followed who they thought had bvFTD, but they didn't progress. They were very slow, and never, ever developed a pathologic FTD syndrome that led to death. They hypothesize that this group of people - and they looked at them clinically, who are these people who don't progress? They tended to be men. Almost all of the cases were men. We're a little different at UCSF, I'll say a word about that. The FTD progressed ever so slowly. This is often a very fulminate disease, where a clinical syndrome begins and you see death in four or five years or six years. So they said, "These are people who are very, very slow." They also hypothesize that in some of these individuals, the partner didn't quite know the person well - sometimes second or third marriages. They thought some of these individuals had mild progressive behavioral disorder on the spectrum of autism, but they didn't really know. They presented this as an ongoing mystery. When the C9ORF72 mutation was uncovered in 2011, we went back to [the data] - we had four patients who had bvFTD phenocopy and two of them actually had the C9ORF72 mutation. John then looked at his data and found a number of his cases also had C9ORF72 mutations. It put into context a number of these people and it pointed out to us a unique feature of C9ORF72. That it can be very slow, very slow and you can follow somebody with this mutation over many years. We have one woman we have

followed for 14 years who has not progressed from a mild syndrome into a full degenerative phenotype. This is a feature of C9ORF72.

The other thing that makes them a little bit more difficult to diagnose is that they don't tend to have the profound frontal atrophy that the other forms of FTD do. These are people that are really a conundrum to us in the clinics. Let me say a word about what some of the really non-FTD phenocopy cases are like. I have called this “phenocopy by proxy”. This is a spouse who wants to put their spouse into this category of bvFTD. They may be in the middle of a divorce, they've read about the criteria. Sometimes when the two come together into our clinic, the team thinks that the partner is more like FTD than the actual person that has been diagnosed. I've called this “Munchausen bvFTD by proxy”. It's a misinterpretation of the history that we are very dependent on.

Another is somebody, and sadly some of these people get a huge amount of publicity, who [has] convinced themselves that they have bvFTD and they make films about themselves. Talk philosophically in a way that no one with bvFTD could ever talk. This is more along the line of Munchausen syndrome. That's another subtype of this. Then there are these psychiatric cases that are really a conundrum. People who develop - just saw one in my clinic last week - new onset of paranoid disorder. It's been slow, but probably progressive with executive loss. Am I sure that that's going to be true bvFTD with pathologic change and neurodegeneration? I'm not sure, but it might be. We do see people with late life schizophrenia-like presentations, bipolar presentations, where maybe it's a primary psychiatric disease. But, beware of phenocopy because we know that if you get the right molecular - you know, it's a cloud of uncertainty. We're not as certain when we call someone a phenocopy. But don't rely on this as reliably not-FTD. You may be surprised.

John Bellone 37:07

I guess it is some hope maybe for patients. We can say there are a subset of people who don't progress. I'm wondering if we have any sense of how often a diagnosis of possible bvFTD turns out to be a phenocopy syndrome? Do we have any idea?

Bruce Miller 37:27

In good centers, it's kind of small. But, of course, it really depends on how broad the population of people you see. We've broadened, in my research program project grant, people that we see until late life psychiatric disorders. If you're looking at new

onset, late-life psychiatric disorders that might be bvFTD, you're going to have far more of them that aren't bvFTD than if you just look at neurodegenerative syndromes. But if you have a full blown bvFTD syndrome, usually the person has FTD, real FTD.

Ryan Van Patten 38:08

John had referenced a possible bvFTD diagnosis. I've read a little bit about the reliability and accuracy of probable versus possible where we can have quite a bit more confidence with probable bvFTD if the neuroimaging evidence is included and there's some functional decline. Of course, if we can look across time and see that someone has declined over the years, that suggests pretty strongly that it's not phenocopy or a psychiatric condition. Can you talk a little bit about how much confidence you placed in possible versus probable?

Bruce Miller 38:44

A great comment. When the atrophy is present, we're pretty confident. I mean, the degree of atrophy that we see in bvFTD is far beyond what is present in typical psychiatric disorders. Caveat, it's the TDP-43 group, FTD, ALS, the atrophy can be more subtle, and sometimes even more posterior. That group, we're often on ice, slippery ice, when we try to decide, just based on the clinical criteria alone, whether this is real bvFTD or something like a phenocopy. That's one group where we're really not sure. Again, there's this big cloud of uncertainty that I'm fascinated in. This was really the beginning of my research when I started on faculty at UCLA in 1985, these people who develop new onset psychiatric disorders after the age of 50 or 60. The etiology for those, in some cases, is going to be bvFTD, but in many cases not. And again, I think your point of these people do not show the severity of atrophy that we see and bvFTD. The other thing that is often helpful is often not there, but is motor changes. If you see someone with a progressive ALS, you can pretty much rest assured that, if they have a behavioral syndrome, it's due to bvFTD. The same was true with progressive Parkinsonism. If someone has progressive Parkinsonian changes, along with a behavior disorder, they are very likely to have tau as an underlying pathology or sometimes TDP-43.

John Bellone 40:43

Would you lump some of the Parkinson's plus syndromes in that bucket?

Bruce Miller 40:48

I do. Again, when I was at UCLA, I became known as a place to refer FTD cases and I started seeing a lot of referrals of people who had a bvFTD syndrome but also

had the eye movement abnormalities characteristic of PSP. And by the same token, I started to see people with sometimes asymmetric, sometimes symmetric Parkinsonism, who I classified as corticobasal degeneration. Phenotypically, most corticobasal degeneration cases present in the FTD spectrum, a lot of them bvFTD. In our brain bank, Suzee Lee did a study of half confirmed corticobasal degeneration, about a third progressive nonfluent aphasia, about a third bvFTD, and about a third executive motor deficit. Corticobasal degeneration falls firmly within the FTD spectrum of diseases and is a tauopathy. PSP, similarly, a pure tauopathy, at least pathologically. These people present with, usually I believe, no definitive paper on this yet, but most people with PSP present with a behavioral or a language syndrome before they actually develop trouble with movement. You can go back to John Steele's original paper on PSP and he realized this. He talked about the prodrome of these patients, which was usually psychiatric.

Ryan Van Patten 42:42

Let's move more explicitly into the clinical syndrome of bvFTD. Now, personality changes are the hallmark symptoms. You mentioned earlier disinhibition, apathy, or inertia, diminished empathy, compulsive or ritualistic behavior, and hyperorality, these dietary changes, these are all part of the 2011 criteria. These behavioral symptoms really hit the core of who people are and can have a devastating impact on relationships with a spouse, family, and friends. Will you talk to us about each of the categories of behavioral symptoms and describe what they look like? Feel free to sprinkle in any stories or anecdotes you have about your work with patients.

Bruce Miller 43:27

Really well said. The disinhibition has been a hallmark of bvFTD. Even in the 1950s when Europeans were talking about Pick's disease, this is a hallmark of bvFTD. None of these behaviors are random. They're all driven by a very specific anatomy. Howie Rosen showed that if you quantify disinhibition as a core feature of your patient, expect to see atrophy in the orbitofrontal cortex, and later he showed ventral striatum. There is a very specific circuit in the brain that is involved with inhibiting behaviors. If you lose that circuitry, you are no longer inhibited, socially correct.

So what do you see? You see, first of all, addictive behaviors. About 5% of our bvFTD patients develop drinking alcohol, which is often thought to be the cause but that's wrong, as a form of disinhibition. David Perry has written about some patients who have all three sorts of behavioral disinhibition - sexual, eating, sometimes gambling. I had a remarkable experience. When I just started studying FTD, I saw

someone who was referred to me from the South. They had been head of a major foundation and got arrested for driving under the influence of alcohol. So they got arrested, and I'll come back to that in a minute. Rather than accepting the arrest, they got into a verbal and physical altercation with the police. Imagine a president of a major foundation who does this. They agreed that this was an addictive disorder and they sent him to a rehab center. His wife was very much against psychiatric interventions. She told me, "Well, I hate those rehab units." And I said, "Why? You know, I think they help people." And she said, "Well, my loved one, he went in there with an alcohol addiction and he left with an addiction to smoking cigarettes. He gained 50 pounds, and he started chewing tobacco." What she pointed out is that when you lose function in the ventral striatum, orbitofrontal cortex, you are addiction and disinhibition prone.

In our studies, the right side seems to be much more important. Why that is? I don't think I know. But in particular, right orbitofrontal cortex atrophy dysfunction really predisposes even the most socially correct person to disinhibition. What do you see? We've read in papers, Madeleine Liljegren was first author on one, she showed that almost 40% of people with bvFTD committed an antisocial behavior that either did or could have let them become arrested. These are often silly crimes. A woman I was working with was riding her car, a policeman was sitting at the light, she went around him, went right through the red light. The policeman was absolutely baffled. He said to her, "I was sitting there, why did you go through the red light?" And she said, "Well, I had to shop. I needed to get some shopping done." Sometimes these compulsions to seek rewards coupled with the inability to suppress a behavior leads people to get arrested.

Disinhibition is the most obvious. People approach strangers, sometimes children, which really alarms the parents of the children and can even lead to the arrest of the person. Some people urinate in public. There's a whole panoply of dissonant behaviors that are very core bvFTD.

John Bellone 48:09
Sorry to interject super quick. I had a patient who brought a prostitute to his family home and just didn't understand why that was inappropriate. [laughs]

Bruce Miller 48:17
Yes. It's an utter lack of insight into the consequences of these behaviors. Absolutely. I'll give you a very similar example. I had a patient who got fired from his work. And what was the reason? Well, he used money in the kitty at work to get a

massage every week. Why did he use the money in the kitty? He didn't want his wife to know. Well, he gets fired, of course, because he's embezzling money from the kitty and then on top of that his wife learns anyway. It's a combination of really bad insight, real inability to project the consequences into the future that can lead to real catastrophes. These people have to be protected because often the disinhibition hurts them far more than it hurts people in the environment. Never violent. I'm sure there'll be examples, but I haven't seen one.

John Bellone 49:22
Yeah.

Ryan Van Patten 49:22
And their loved ones, of course, a spouse or close family members are often baffled and just so upset and terrified at this person who they used to know and the actions that they're committing now.

Bruce Miller 49:36
Absolutely. It's really catastrophic. It can sap family resources, this reward seeking without understanding the consequences of the reward seeking.

Ryan Van Patten 49:51
I imagine that many people out in the world aren't aware of bvFTD. Take a spouse who's married to a 45 or 50 year old person and these behaviors start happening. They aren't going to know offhand that, oh, this is a brain disease that is causing these behaviors. The education that we can give them will be very important.

Bruce Miller 50:15
Absolutely. Not only the families, sometimes the people at work who deal with these individuals in HR. One of my first patients was accused by 27 women at work of sexual harassment and he denied it vigorously. These are the sorts of things that end up in HR and misunderstood by the courts. We tend to not really associate behavioral disturbances with brain disease. I think psychologists like you, Ryan and John, and people in our field are going to change the way society has a perspective on this.

John Bellone 50:55
Yeah. There's a very fuzzy line between neurology and psychiatry that people don't realize.

Bruce Miller 51:01
And FTD is where it is.

John Bellone 51:03
Yeah, true.

Bruce Miller 51:05
That fuzzy line exists. I might comment in particular on three other aspects of this criteria. The second is apathy. A lot of people begin with apathy, inertia, loss of drive. The apathy can be motor, they move less. The apathy can be emotional, they're unconcerned about people in their family. And the third can be apathy about the future. No planning, organization for future activities. This apathy is really driven by dorsal frontal pathology, anterior cingulate. If the disease is more dorsal, apathy is a very prominent feature. A lot of people with apathy that precedes anything else have corticobasal degeneration or progressive supranuclear palsy because these diseases affect that dorsal circuitry more than others.

The loss of sympathy/empathy is, for me, one of the most fascinating aspects of bvFTD. Kate Rankin, a psychologist at our place, an incredibly creative one, has shown that if you are judged by your loved ones to have loss of empathy, concern for others, you will have degeneration of the right anterior temporal lobe. If loss of empathy is the first feature of the illness, it is almost always right anterior temporal. Isn't that amazing? That a psychiatric syndrome like sympathy and empathy is driven by a circuit in the brain, a social circuit on the right side, that is involved with looking at other people's faces, thinking about what they're feeling, and then doing something in an appropriate way.

You can break down the deficit. For some people it's really a very perceptual one. They really can't see the emotions on people's faces and that is part of the loss of empathy. Virginia Sturm has written quite a bit about the feeling of empathy. She has shown that bvFTD patients with loss of empathy have a very profound loss of an autonomic response to films that should increase emotion. If they see a movie that should evoke sadness, we see no autonomic response, no changes in the face that should suggest that they are sad. Same with disgust. People with FTD do really disgusting things, in part, because they don't feel the disgust that we all do when we might try to eat food off another person's plate or pick something up off the ground and put it in our mouth or in our pockets. These are really core features of right anterior temporal degeneration as part of bvFTD.

Ryan Van Patten 54:27
An interesting example of the loss of empathy that I've read about is a person with bvFTD witnessing another person crying and asking, with no sarcasm, "Why do you have watery eyes? What's going on there?" They truly don't understand what that is. That's remarkable.

Bruce Miller 54:48
It really is remarkable. It takes your breath away. There are two situations where this becomes diagnostic. One, I just saw this at a recent clinic. A gentleman, a dentist, his daughter dies, she's aged 40. And at the funeral he says to people, "Well, it's just as well. She was really troubling for all of us." When I interviewed him, I said, "Must be a hard year for you because of the loss of your daughter." And he said, "Oh, no, it's good because she was quite a lot of work." I think these breathtaking comments at funerals are often truly diagnostic.

Ryan Van Patten 55:36
Yeah.

Bruce Miller 55:37
Yeah.

John Bellone 55:38
I wanted to go back to what you were saying about apathy. It can be difficult to parse that out from true depression. Do you have any pearls of wisdom for clinicians about how to deal with anhedonia as part of depression but also as part of this bvFTD syndrome?

Bruce Miller 55:58
One of my comments would be to describe the phenomenology and don't over interpret it. When you see someone who is moving less, who is speaking less, it might be a mood disorder. It always helps to ask the person, "Are you depressed?" And no surprise, a lot of people who are truly apathetic say, "No", they're not. So I look very carefully at the screening questionnaires. You and I know that there are people who are depressed who don't realize it. But with apathy it has a very different quality. Describe the phenomenology and don't over interpret it. If there's uncertainty, there's no doubt you must evaluate this person for bvFTD.

Ryan Van Patten 56:54

Similarly, the compulsive and ritualistic behavior that is part of bvFTD can certainly overlap with OCD, in particular the C. I'm wondering about the differential diagnosis there. Based on what you just said, I imagine that people with bvFTD don't have as much underlying anxiety, obsessive thoughts. They're not distressed and troubled by their symptoms. Is that accurate?

Bruce Miller 57:20

Absolutely. In OCD we think of obsessions and compulsions. In bvFTD, the compulsions are evident. The obsession, not so much. Often it is a repetitive behavior, sometimes without any evidence of compulsivity. These individuals have a hard time describing why they are doing compulsive things - collecting coupons, putting objects in a certain order. It's pretty rare with bvFTD to have the typical OCD compulsions - worry about germs. In fact, it's often the opposite. The compulsive nature of this is helpful. The age of onset, of course, is helpful. OCD is not a disorder that ordinarily begins in the 50s or 60s. Those are some of the things that really help us.

Ryan Van Patten 58:23

And then to round out these behavioral changes, we can talk about hyperorality and the dietary changes. I know we've learned more in recent years about physiological alterations in bvFTD related to metabolism and you've mentioned autonomic functioning. These are mediated, in part, by the hypothalamic neuroendocrine systems. What's the current understanding about how the underlying disease is impacting the systems? What are the symptoms that we can expect to see?

Bruce Miller 58:54

Hyperorality occurs, in our cohort, in about 60%. So about 60%, they overeat. That's usually the major feature. They can be more broadly hyperoral - putting things in their mouth, like smoking, but usually it's eating. But stay aware for other evidence of hyperorality. When we first studied this, Josh Woolley, now a faculty member at UCSF in psychiatry, gave people an opportunity to eat 12 sandwiches, and, again, about 60% of the people ate all 12. The phenomenology was very bvFTD. The person would often say after eight or nine, "You know, I'm pretty full", and then put another sandwich into their mouths. It's a disinhibition.

The anatomy is complicated. You can get a frontal injury, in and by itself, that decreases your ability to inhibit behaviors, then you overeat. You can have degeneration in the hypothalamus, Piguet and Hodges showed that that was a

correlate of overeating in bvFTD. Josh also showed that most of the people who overeat with bvFTD had atrophy in the anterior insula, orbitofrontal cortex, and anterior temporal lobe on the right.

John Bellone 1:00:24
It's important for our listeners to realize that these are part of a constellation of symptoms, right? If your husband is overeating, [laughs] he probably doesn't have FTD. It's part of a syndrome with multiple of these types of symptoms. I think it's important to remind people of that.

Semantic dementia subtype of primary progressive aphasia is one of the related neurodegenerative conditions that can come with changes to behavior or personality. Do you want to say anything about the overlap and differences between bvFTD and semantic variant PPA? Just a broad overview.

Bruce Miller 1:00:58
Fascinating question. If you degenerate the anterior temporal lobe, which is what Pick described in 1892, usually the pathology is TDP-43. Bill Seeley has a nice paper on this from around 2006. The atrophy typically begins on the left side, so you have trouble naming objects. Then it spreads to the right side, anterior temporal, you have trouble recognizing faces, you lose empathy. Then almost immediately it sweeps in the orbitofrontal cortex. Pretty early on, particularly if the FTD is more right sided, you see lots of behavioral disorders that emerge. There's a lot of overlap with a semantic variant. They're very disinhibited before very long.

John Bellone 1:01:55
It sounds like the time course of the symptoms can help distinguish these.

Bruce Miller 1:02:00
Absolutely.

Ryan Van Patten 1:02:01
We'll move into cognition in a moment, but this differential diagnosis of bvFTD versus psychiatric conditions is so important. I wanted to ask one more question relating to the collateral source of the patient and just how important they are for us as the clinician. Can you talk about their importance broadly? Also how important it is for the collateral source to have known the patient for a while, like multiple years, in order to track their decline over time.

Bruce Miller 1:02:33
Great question. Caregivers or spouses or children vary enormously in their ability to observe and tell an accurate history. Sometimes we're very constrained when a family is insistent that these behaviors are not present, or that there's another explanation for the behaviors. This makes diagnosis sometimes harder. If you have a great historian, you're really set. Some of the problem with phenocopy is this exact issue - the observer isn't very good. You hope that on your examination you can confirm aspects of the history by observing behaviors. But I would also say that sometimes people with frontal disorders can really pull themselves together for a short period of time. I've learned, as I've gotten older, I see less disinhibition when I work with these patients. It's the research coordinators that see it. The younger ones, where sometimes the patient feels more comfortable and is evidently much more disinhibited. It'd be nice if the history was affirmed at the bedside, but sometimes it just doesn't happen.

John Bellone 1:04:06
Let's transition into talking about the neuropsych testing of these patients. Can you talk about the measurement of cognition in bvFTD and what's most important here?

Bruce Miller 1:04:18
In the national research criteria, we said loss of executive function with sparing of visual spatial skills and sparing of memory. I battled fiercely, I'm the senior author on the criteria, but I lost. I wanted not to have sparing of memory as part of the criteria for a couple of reasons. One, a lot of FTD patients actually have pathology in the hippocampus, particularly the TDP-43 variants. They have a real memory deficit and a real reason for it. The other [reason] is psychologists, good ones, know that you can have a frontal disorder and have trouble with memory as well.

Visual spatial sparing is pretty darn common. If you've got somebody who is profoundly impaired functionally and they draw a pentagon perfectly, that's classic neuropsychological evidence of bvFTD.

Typically we see loss of executive function early in bvFTD. You see things like trouble with generation, we use D words, that's often altered. Working memory, digits backwards, is often impaired in people with bvFTD. These are tests that are fairly sensitive to most bvFTD. There are some people where the disease begins only in the paralimbic cortex and doesn't get out into the executive parts of the bvFTD until later. Those people might do brilliantly on executive functions. I remember I had a gentleman, a physician, who was in a nursing home, profoundly

functionally impaired. All he did every day was just watch the airplanes and count them coming in and out of the airport that was near the nursing facility. He did brilliantly on all tasks of executive function. Unable to look after himself, put clothes on, but still had sparing of executive function. That's unusual. Most of the time, when somebody reaches us, they have real deficits. In word generation, [letter fluency is] often worse than animal [fluency] unless it's right temporal. And then also trouble on tasks of inhibition. Stroop test is a good one to capture this loss of inhibition. [For] future planning memory, I always like to ask my patient, "What are you looking forward to in the future?" They may be dying of ALS, and they don't have a job, they've alienated their family. What are you planning for the future? "Well, I'm working." Well, they're not working. "I'm really looking forward to spending this time with my family." This inability to see what the future holds is very characteristic. We also ask our psychologists, and they do it really well, just to check off what you observe during the examination. Was there disinhibition? Was there apathy? Were there inappropriate comments? The observations that the psychologists make are almost as important as the testing of the traditional executive function.

Ryan Van Patten 1:08:03

This memory issue is very important. Clinical lore could suggest that if you are examining an older adult and the differential is FTD versus AD that if there is a poor memory profile, it's AD. If there's a poor executive profile, it's FTD. But it's not necessarily that simple. It's really important for us to be aware that patients with bvFTD can have memory impairment. I'm wondering if there is a specific memory profile that might suggest AD versus bvFTD. For example, I've seen a little bit of evidence suggesting that topographical or visuospatial memory might be more specific to AD versus FTD. Is that accurate?

Bruce Miller 1:08:51

There's so much variability on this that sometimes it's hard for me to generalize in a way that's helpful to people. I would say the one thing - Kate Possin, our neuropsychologist, wrote a nice paper where one of the big differences was perseverative errors. If you give someone a word list, and they throw in 15 unrelated items, that's much more typical of bvFTD than AD. Just counting up the perseverative errors that someone makes, may be the most reliable difference in people with Alzheimer's who have frontal disease. The big difference between the behavioral variant of Alzheimer's disease, and Rik Ossenkoppele just wrote a nice paper on this, is the involvement of parietal lobes in Alzheimer's but sparing in bvFTD. That's a big difference and that's why visual spatial sparing is so typical of

bvFTD. If you have a patient who can't copy, beware of a diagnosis of bvFTD. It happens, and the disease can spread more posteriorly in some cases, but usually it's so focal. I don't think you need much of the brain at all, except for the parietal lobe, to make a nice copy on paper.

Ryan Van Patten 1:10:30

Those perseverative or self monitoring errors in bvFTD really fit with the rest of the syndrome as we've talked about today. I'd like to hear you talk a little bit about the NIH-EXAMINER battery, this newer computerized battery of executive functions that's based on methods from item response theory. As I understand it, it's been designed to be an endpoint in clinical trials. The evidence I've seen is promising, suggesting that the NIH-EXAMINER might be more sensitive to early FTD, even in familial cases, than are the traditional paper-pencil neuropsych tests of executive functions. What can you tell us about the EXAMINER?

Bruce Miller 1:11:13

This was developed about seven, eight years ago. Joel Kramer got a group of experts together - real experts, just brilliant neuropsychologists from across the United States - and asked them for their ideas about what is the future of testing of prefrontal cortex. He asked specifically that these tests would have a specific anatomy. That they would be helpful in separating one disease from another, that you could have multiple variants of this, so you could use them in clinical trials without worrying about learning effects. It's an excellent system. They have some social cognitive measures that are very nice. This is indeed very promising.

I don't think we can make the mistake of just using the tests for Alzheimer's disease that have been used for clinical trials. And we are there with clinical trials. We need really great neuropsychology as part of the assessment of the change. Just a comment about that. So, the loss of executive function may not be specific to bvFTD. You see a lot of this in early Alzheimer's as well. But longitudinal progression may be much more powerful than the behaviors, which are sometimes already set because of the massive degeneration in the insula, anterior cingulate, orbitofrontal cortex. The executive tasks may be very, very good markers of the efficacy of a clinical trial.

John Bellone 1:13:05

Just to clarify, those with FTD would decline much more sharply in terms of the executive functions?

Bruce Miller 1:13:12

Yeah. Sometimes they've reached a floor in behavior. Sometimes the behaviors, like on the Neuropsychiatric Inventory, sometimes it actually gets better as somebody develops profound apathy and that wipes out the disinhibitions, the compulsions, etc. The behavior is really good for helping early diagnosis. But the executive loss can be fairly subtle when someone is rendered in a clinical trial. Dave Knopman has shown that things like letter generation may be pretty sensitive to progression.

John Bellone 1:13:55

Gotcha.

Ryan Van Patten 1:14:06

bvFTD is more common in men than in women, on average. Are there other differences in epidemiology, neuropathology, or clinical symptoms across sex, race, or other person characteristics that we know of?

Bruce Miller 1:14:20

We have found that at UCSF it is more common in men. Other people have challenged this, so this remains to be seen. Illán-Gala, in Barcelona, has written a little bit that women seem to be a little less sensitive to atrophy in the prefrontal cortex than men. They can have more atrophy with the same degree of behavioral disinhibition. If you want to generalize this into a stupid idea, well, men are just more disinhibited. Their prefrontal cortex is a little bit less developed than women. That's what my teacher Frank Benson always taught me.

John Bellone 1:15:06

That's what my wife says, too. [laughs]

Ryan Van Patten 1:15:09

[laughs]

Bruce Miller 1:15:11

So that's one thing. We have huge questions about the geography of bvFTD. Some of the mutations, like C9ORF72, that we see commonly in the West and Northern Europe, United States, Australia, are not very common in Asia. We don't know anything about Africa yet. There are very few bvFTD cases diagnosed in African Americans. Could this be because these populations don't carry the same

mutations that Caucasians do? Don't know yet. There just isn't enough data collection yet. We're working in South America where we hope to answer some of these questions. So, in Peru, a large percentage of people are indigenous. We don't know anything about whether indigenous people have mutations. In Brazil, lots of people originally descended from Africa, who are now part of the population. We're going to just get a huge amount of data about bvFTD in different ethnicities. I believe the data from Korea, I think it's well done, they do not see a lot of mutations in tau, progranulin, or C9ORF72.

John Bellone 1:16:34

Before turning to interventions, I'm curious if there's anything that you might improve or change about the 2011 Rascovsky criteria, other than the memory component, which you had already mentioned.

Bruce Miller 1:16:49

We would love to see scales that psychologists could use to capture disinhibition at the bedside, but also from behaviors described by loved ones. I'd love to see quantitative scales for loss of empathy. Kate Rankin has a number of scales like the IRI that we think capture some of this. Complemented by scales, the clinical observations will be important. I like the criteria. We should probably include a negative amyloid biomarker. It was almost there in 2011, but I think that would be important as part of the criteria. No evidence of amyloid positivity. In these early clinical trials, we probably don't want people with dual pathology. It happens, but we certainly don't want people with Alzheimer's disease in these clinical trials. Our biomarkers for Alzheimer's are so good right now that we can use that in the newer criteria we eventually develop.

Ryan Van Patten 1:18:08

What do these behavioral disinhibition scales look like? It would not be a self-report scale we give to the patient, right? Is the clinician observing the behavior of the patient? Is a collateral source reporting on their behavior? Or both?

Bruce Miller 1:18:24

The NPI at the moment is our best scale for disinhibition. It's purely observer based, by the caregiver. Our psychologists have a checkoff - Did the person interrupt? Did the person say things that were socially inappropriate? Was the person blunted in affect? Did they reach across and touch the examiner? Did they say things that were inappropriate? This sort of checkoff is helpful, but the gold criteria for disinhibition currently is the Neuropsychiatric Inventory.

Ryan Van Patten 1:19:07

That makes sense. Let's move into treatment and intervention now. You had alluded to this earlier, unfortunately, there are currently not any disease modifying treatments available for bvFTD. So we're left to manage the symptoms of the disease. Let's start with medications. We know that typical Alzheimer's medications like cholinesterase inhibitors and Namenda are not effective. But I've seen a more mixed literature about SSRIs, psychostimulants, and antipsychotic medications. What are your thoughts?

Bruce Miller 1:19:42

I have a very fixed idea about this. Some of the things that I've done in patients that have been [the] most helpful is taking away cholinesterase inhibitors, taking away drugs with psychoactive effects. That's the first thing you do. Look at the medicines - are they really needed? Cholinesterase inhibitors, in some people, can really trigger disinhibition. It can be gratifying to take that off.

Antipsychotics have a different problem. They blunt people quite a bit. They bring out the movement problems in people with bvFTD. They increase apathy, increase inattention, increase the likelihood of falls. Certainly the typical antipsychotics we avoid because of their effect on movement.

For the SSRIs, the data is mixed, but definitely worth trying. Some people really have a rather dramatic decrease in their irritability, outbursts, sometimes overeating and compulsive behaviors. Changing serotonin in the brain, which is profoundly deficient in bvFTD, can help these patients.

I am worried about stimulants. One of my first cases that I ever treated, I didn't do it, ended up in the hospital in delirium because his doctors had put him on stimulants. Sometimes families come and say, "I really want to do something about the apathy." And sometimes, in the back of my head, I think, "Do you really want to do something about the apathy? Do you want to replace it with wild disinhibition?" In general, I don't think the data is there and I don't use the stimulants.

Again, anticonvulsants [there's] not a wit of data to support their use. So we're mostly on the antidepressant area, unless someone's behavior is so disturbing to family, to loved ones, that you really need to increase their apathy. And, there, antipsychotics work.

Every three or four months [I am] reconsidering the package of medicines that somebody is on with the idea of removing rather than increasing them. A lot of the

good that we do with patients isn't pharmacologic. It's helping their family develop strategies to protect the finances, to protect the individual from getting hurt. Prevent them from doing antisocial things that could lead to arrest. A lot of it is environmental.

John Bellone 1:22:44

That was going to be my next question. There are non-pharmacologic interventions that have shown some efficacy in improving outcomes in these patients - environmental modification, like you mentioned, caregiver education, exercise, potentially OT, PT, speech therapy. I'd like to talk a little bit more about these in detail. Maybe it's best to start with caregiver-based work because it's so important to include loved ones and caregivers early in this process. If we imagine that we just made a new diagnosis of probable bvFTD, what should the psychoeducation of family members and caregivers look like?

Bruce Miller 1:23:22

Explaining is really the first step. "This isn't your fault. It isn't your loved one's fault. It's driven by a change in the brain, and we behave based on the function of our brain."

Also support. These people are under tremendous siege. A lot of times people in the family criticize the way they've managed things, blame the magnificent caregiver for the bad outcome. I often start by saying, "You know, you have done a tremendous job of dealing with a very hard problem. It is one of the hardest problems in all of neuropsychiatry, having someone with a progressive behavioral disorder." So I think support, big support.

Discussing behaviors in a rational way. What are behaviors that really don't matter very much, and what are behaviors that are really dangerous? Thinking through with caregivers what you got to do. Taking the car keys out of the hands of the patient - very, very helpful. Thinking about their spending of money - limiting it so that it doesn't do damage. This is a massive planning process.

Recovering hurt feelings. Imagine being a teenager and suddenly your father doesn't care a bit about you. The children don't understand this. It's profoundly hurtful. Getting them to understand that, really, this isn't the fault of the person. Sometimes I go and think back about - recently thinking with some kids who had a father who died of bvFTD syndrome and getting them to think back to what their father was like before the illness. I think it can be very helpful.

Jennifer Merrilees, one of our nurses that's worked a lot with Bob Levinson and Virginia Sturm on interventions, meditation, that can diminish the emotional response to the bvFTD patient. Virginia has written about “Awe Walks”, which I think are spectacularly successful. Getting someone to walk out in nature, thinking about the glory of our existence, and doing this a few times a week has remarkable positive effects on caregivers.

These are some of the things that we think about systematically. Making sure that every bit of attention that you spend on the patient is also spent on the caregivers. "Can we get respite into the house? Are you depressed? Do you need an antidepressant?" We have shown a very high prevalence of psychopathology in caregivers of people with bvFTD. So this is important work.

John Bellone 1:26:29
Are there any publicly available resources or information that you think would be helpful for our audience to be aware of?

Bruce Miller 1:26:38
Absolutely. The AFTD, the Association for Frontotemporal Dementia*, had a powerful impact across the world. Looking at their website and talking with people there can be helpful. We are very devoted, at UCSF, to families, caregivers and we are always available to think about this. There are also great centers across the United States and across the world that are interested in this and can be helpful. Our website has quite a bit of data that can be very informational for families.

*Transcribers note: The Association for Frontotemporal Degeneration

John Bellone 1:27:18
Given that you mentioned your UCSF clinic, how often do you think clinicians should refer to a specialty clinic after making a diagnosis? Do you think that's helpful?

Bruce Miller 1:27:30
Gosh, I really do. I have huge respect for primary care physicians, psychologists, but I think a multidisciplinary team is really needed to care for this very complex disease with pharmacological therapies down the line.

Ryan Van Patten 1:27:55

Talk a little bit about environmental modification. You mentioned taking away car keys as being one good idea. And also about the Tailored Activity Program and its evidence for efficacy.

Bruce Miller 1:28:07

We're dealing more now with common sense and really strong data supporting interventions. The interesting thing about this is each family needs different interventions, which sometimes makes it a little hard to study. A patient I saw a week ago, [the] family was very worried they were watching pornography in public, which is embarrassing. But increasingly worried that pornography involved younger and younger people. So what has gone from private, no one knows, then the family knows, then it's in public, and then there's potential for arrest. So in that family, the pornography was the major issue. In other people, it may be approaching strangers. In other people, it may be a compulsion to urinate in public. These multidisciplinary teams, often the nurse and sometimes psychologists, are just brilliant at this. [They] think with the family about the best ways to intervene. It's very valuable.

I'd love to see music therapy formally studied. Buyakada (?) in Japan has done some work in this space. We work with art in patients with bvFTD and we see some magnificent products. If you can get a patient focused on a compulsion that is associated with aesthetic outcomes, this is a very good thing. I don't think we have the answer yet. I don't know, Ryan and John, if your experience tells you certain interventions are tried and true, but we do a hodgepodge of things.

Ryan Van Patten 1:30:08

Right. I definitely like the idea of tailoring the environmental modification to the patient and the specific symptoms that are most problematic for them - the behaviors. Can you briefly describe the Tailored Activity Program? I've seen a little bit of evidence supporting it.

Bruce Miller 1:30:25

I may not know exactly what you're referring to here.

Ryan Van Patten 1:30:30

Maybe it's a much more niche intervention that's not as widespread. [laughs] They say you directly target a specific behavior and redirect it into a personalized and relevant activity selected by the caregiver.

Bruce Miller 1:30:44
I think that's a great comment.

Ryan Van Patten 1:30:52
I wanted to ask one more question about intervention, which is around molecular therapies. You had mentioned this earlier in our conversation. What's the work being done here? Could I start to consider the word "cure" or "disease modification" for FTD?

Bruce Miller 1:31:09
I'd love to hear the word "cure".

Ryan Van Patten 1:31:12
Yeah.

Bruce Miller 1:31:14
When we start to think about slowing progression - by the time we diagnose someone with bvFTD, the state that they're in is sometimes so awful that I have loved ones say to me, "I really don't want to preserve the person in this state." So where are we thinking about a cure? We're thinking about a cure in the genetic forms where we can follow a gene carrier from asymptomatic into early disease.

Depending on the molecule, we really have potentially curable approaches. In the case of tau, you could use something like CRISPR, or an antisense oligonucleotide to stop the function of the bad gene. You might have a really powerful prevention. We know that, in mice models, if you completely knock out tau, it doesn't seem to cause too much, if any, clinical change. So we can definitely, if we could cut out that mutation in tau. People like Jennifer Doudna, one of the inventors of CRISPR, are bringing this technology to the brain. If we could cut out the mutation in the brain, I think we would prevent this illness. Very exciting future for gene carriers with tau.

Progranulin, slightly different approach. With progranulin, a number of groups have shown that they can deliver progranulin on top of a transparent molecule into the brain. And in theory, because this is due to a deficiency of progranulin, could suddenly prevent the abnormal cascade of inflammation lysosomal dysfunction that we see in progranulin mutations. That's about ready to start, those replacement therapies. Very exciting. Also trials going on now that are focused on increasing the amount of progranulin in the brain indirectly.

With FTD ALS, we have a large hexanucleotide repeat gene. If we could cut that gene out with CRISPR, turn it off with an antisense oligonucleotide, get enough of it into the brain to really stop this molecular cascade. I love your phrase, we're talking about cures.

I believe that the first degenerative diseases that will be cured are the molecular forms of frontotemporal dementia. Lots of excitement in lysosome proteasome. We know as we get older, our cells have a harder time getting rid of misfolded proteins. If we could kick up the machinery in the cell to increase the degradation of bad proteins, we might really prevent these diseases, even the sporadic forms. Lots of really smart approaches. We started studying this late, but wow am I ever excited every time I talk to the basic scientists about what they might do.

Ryan Van Patten 1:34:40
Yeah, this is very exciting.

John Bellone 1:34:42
Yeah, real hope for this really challenging disease.

Bruce Miller 1:34:45

Won't it be amazing for us neurologists, psychologists, neuropsychologists in particular to watch someone with a behavioral disorder who suddenly awakens like Oliver Sacks talked about?

Ryan Van Patten 1:34:59
Right. Yeah, a lot of hope.

Well, Bruce, this has been a tour de force of bvFTD. Thank you for the knowledge and wisdom and your time. Before we let you go, we have two quick questions. We call them bonus questions about neuropsychology. You're a neurologist and you work closely with neuropsychologists so I'm very interested in your thoughts. Our first is: If you could improve one thing about the field of neuropsychology, what would that be?

Bruce Miller 1:35:30

More consistent and better quantification of behavior. That's a big one for bvFTD. I also think that we have done so much virtual during this time of COVID that it has opened my eyes to the possibility of in-home testing, tablet-based testing that we

can do remotely. It's so hard to bring someone from remote areas in California or across the world into a university. Particularly true for minorities, underserved populations. Being able to do this remotely, I think, is a grand challenge for all of us.

Ryan Van Patten 1:36:18
I completely agree. John and I have talked about this issue with a few people on the podcast - Russ Bauer, Bob Bilder, Laura Germine, Tom Parsons - there are neuropsychologists working on this, and I think it's so important to focus on.

Bruce Miller 1:36:34
Fabulous.

Ryan Van Patten 1:36:34
Yeah.

John Bellone 1:36:35
The last question we have for you is asking about one bit of advice you wish someone had told you when you were training, or maybe someone did tell you, that really made a difference. Just an actionable step that trainees can take.

Bruce Miller 1:36:49
Very early on when I started studying FTD, I began to realize that it was the team around me that was really important for bringing solace to families with bvFTD. It was the psychologists, the nurses, sometimes social workers, spending time with the family as well as the loved one. Also probably humility. There is nothing more embarrassing, personally for me, than thinking someone has bvFTD when they have a bipolar illness. So some humility with the initial diagnosis, I think, is really important.

Ryan Van Patten 1:37:33
Great. Well, that does it for our questions. Thank you, again, for being so generous with your time. Really appreciate it.

Bruce Miller 1:37:39
I appreciate what you're both doing. This is fantastic. I'm very grateful.

Transition Music 1:37:44

John Bellone 1:37:48

Well, that does it for our conversation with Bruce. If you'd like to support what we're doing here, please leave us a rating on whatever podcast app you're listening to this on. Be on the lookout for upcoming episodes on intellectual disability, culturally informed neuropsychological evaluations, working memory, clinical case presentations, and many other topics. And, as always, thanks so much for listening, and join us next time as we continue to navigate the brain and behavior.

Exit Music 1:38:17

John Bellone 1:38:41

The Navigating Neuropsychology podcast and all the linked content is intended for general educational purposes only, and does not constitute the practice of psychology or any other professional healthcare advice and services.

Ryan Van Patten 1:38:53

No professional relationship is formed between us, John Bellone and Ryan Van Patten, and the listeners of this podcast. The information provided in Navigating Neuropsychology in the materials linked to the podcasts are used at listeners' own risk. Users should always seek appropriate medical and psychological care from the appropriate licensed healthcare provider.

End of Audio 1:39:11