

Phenotype and Measurement Conference
Hosted by: Borderline Personality Disorder Research Foundation (BPDRF)
Thursday, October 19 and Friday October 20 2006

Meeting Minutes for Day One: Thursday, October 19, 2006

In Attendance:

Marco Stoffel (President, BPDRF)
Andy Skodol (Chair, BPDRF Scientific Advisory Board)
Max Burger (Board, BPDRF)
Jim Breiling (NIMH)

Donna Bender	Rich McNally
Paul Pilkonis	Roel Verheul
Drew Westen	Paul Links
John Gunderson	Emil Coccaro
Joel Paris	Larry Siever
John Oldham	Lee Anna Clark
Leslie Morey	Irwin Waldman
David Watson	Charles Sanislow
Tim Trull	Martin Bohus
Jill Hooley	Robert Krueger
Marsha Linehan	John Livesley
Rebecca Shiner	Mary Zanarini
Tracy Shea	Michael Neale

Welcome from President – This conference idea of Steve Hyman. Andy Skodol will be facilitator. Board wants to assess where we are and where we'll be going for the next few years. Learned a lot, risk takers. Thank you for coming...

Skodol (facilitator's opening remarks):
Columbia University and then moving to Arizona mental health research

The idea for a Phenotypes conference has been around for five years – to get us all together to figure out what we know and don't know about core features of BPD. We asked a number of people to write short papers about features in the main areas: Interpersonal Features; Affective Features and Impulsive Features.

We also want to explore genetics, adversity development comorbidity, treatment etc.

Some people had same assignments others different – core features, different measures and extent to which phenotype meets those criteria.

Invited several people who represent different important perspectives outside our field.

Format is going to be to go around room and make brief 3-5 minute summary of the essence of your paper. Papers are available; we want to move more toward a synthesis and establish a future research agenda

3 symptom areas plus one.

Start with interpersonal, affective then impulsive.

The fourth group is Cross Cutting features. I tried to look at the papers and assign folks to topic areas on the content of their papers. Four groups in morning and one group after lunch then split up into separate rooms and the task of work group session is to synthesize materials from your basic topic area and one member will present back to the group and assemble tomorrow morning. You can create slides, you will have access tomorrow morning and after lunch tomorrow we will have a more practical discussion and decide whether we will have overview paper. But more importantly, we will establish a research agenda.

3-5 Minute Presentations

Interpersonal Features Group:

Bender:

You may be wondering why I was designated to go first. Model 3-5 minute presentation. I am asserting that one of the core features of BPD is fundamental inability to create stable representations with self and other. The BSORD notion grows out of theoretical and clinical traditions that most of you are familiar with – splitting; protecting good from bad; attachment paradigm; neurological perspective that encode...

Cog. Dysfunctional beliefs and underlying maladaptive

Number of measures designed to do content analytical work

The attachment paradigm is popular – insecure attachment paradigms. In cognitive tradition new instrument out schema mode. Proposed phenotype – representations of self and other malevolent, negative biases and attribution area in associating interpersonal interactions that reinforce negative internal reps.

Conscious vs. unconscious- fixed vs. varied, identify key, establish linkages (impulsivity, self destructive acts etc.) delineate process and content associated with BSORD investigate if and how BSORD differs from SORDS with other disorders. Establish definitions for establishing representations of self and others, elaborate phenomenon that has direct clinical relevance. How the patient works with treaters and effects that patient has on clinician.

Pilkonis:

Donna looked from inside out I'm going to start in other direction by arguing that best window is to look at interpersonal behavior because of its transparency. And because of its theoretical coherence. Our work on interpersonal and BPD yields important theoretical and clinical insight by taking attachment perspective. By understanding some parts of the symptoms and patients that have BPD – if you insist on this sort of discipline it's an important stepping stone for diagnosing BPD. Attachment theorists assert that it is a theory about interpersonal relatedness, because lack of emotional regulation is such an important Part of BPD Key insight is that we need to look at both of these areas together. Figure one in our paper; other innovation is not to settle on any single level of analysis but to integrate various analyses. 1. Global assessment of social functioning: Social network examinations and social, cognitive and psycho physiological. We are learning valuable things under the rubric of attachment theory. Wave of future – affective neuroscience as well as other traditional BPD interpersonal descriptions.

Westen:

Focus on interpersonal realm. It is generic to all three phenotypes. Think in terms of how we develop phenotypes. Try to figure out what underlying dimensions with 9 items. Best way is to devise large item set. Interpersonal functioning how well they predict molecular genetics functioning and functioning two years later.

Universal phenotypes and diagnostic criteria:

Do we focus primarily on behavior and internal process or one or the other? I think both if we want to get phenotype right. Phenotype requires this because both wax and wane. Into characteristic or distinctive features. BPD co occurs with many other PDs if we focus on characteristic features – they are highly characteristic of BPD patients but not distinctive. What are distinctive are things in diagnostic criteria now. Informant and method affects think about informants BPD patients are best informants b/c can describe behavior and conscious phenomenology, but cannot capture holistic affect. Think of attachment theory etc. as helping us with the

Gunderson:

Participants are conceptualizing phenotypes in highly variable ways. Phenotypes are observable phenomena that signify psychobiological dispositions with significant heritability. The borderlines interpersonal relationships, like their affective and impulsive factors, are one of the 3 major components of the BPD syndrome. To establish that interpersonal relationships are a phenotype, they need 1st to be distinct and prototypic. The contradictory needy/fearful interpersonal style has always been the most specific aspect of BPD. The 2nd issue is familiarity – interpersonal relationships of BPD have been shown to be familial. The 3rd issue is genetics. Genetic information is not as robust as it could be. John Livesley has shown that BPD's interpersonal issues of abandonment has an inheritability of .55. This evidence indicates that BPD's disturbed relationship style should be reconceptualized as a phenotype.

Paris:

Psychosocial risk factors impact on BPD phenotypes? No. Because Risk factors are things which are more frequent in some conditions but don't cause the condition. Most BPDs don't have these same risk factors. The only thing that makes sense in understanding is that biologically vulnerable people respond more acutely to adverse conditions. We don't really know why these patients have abnormal attachments – common pathways to many different affects? People at Harvard tried to promote idea that this is a complex PTSD. PTSD itself is a flawed concept has etiological factors in DSM. Will benefit from stress diatheses model.

Oldham:

Treatment perspectives Stress vulnerability model is useful. Persuasive model is to consider two of the different phenotypes as core necessary but not sufficient – engines or motors running too fast too hot if combined with insecure attachment, they lead to interpersonal difficulties. Interpersonal difficulties are secondary to the first two insecure attachment can be because of neglectful, or inconsistent care taking. Or that parent is under such stress due to BPDs temperament it affects parenting. Chart outlines typical features of major typical psychotherapies.

Morey:

Dimensional aspects. Various models proposed. Not either/or questions but capturing different slices of overarching continuum that causes troubling behavior. Some are shaped by environmental interactions. For example we find that general personality traits that have high heritability measure over time well but... proximity to problem behaviors: my borderline scale has self aspects separated from interpersonal – one cognitive one interpersonal relationships

They are dynamic and likely to change. My scale fluctuates over time and due to different fluctuations in hormones etc. Moment to moment fluctuation triggers long line of events. We need to focus on those as well. In specific interpersonal relationships how do these traits play out – misrepresentation, mislearning rules? How do the more dynamic traits play out into specific problem behaviors? Most important proximal to distal connection. People portray them as either or but they are capturing different parts of the elephant.

Comments/Questions:

Paris – BPD epiphenomenon of other things? I don't see it that way but am interested in hearing what other people have to say.

Stoffel – Complicated relationship between these three main features. What consensus is there on the model? How do we study that?

John – can't separate relation to self and other. They are enmeshed. These things aren't linear or separable. These things grow up simultaneously and precipitously.

How to show Stress diathesis model? We might also consider heterogeneity. Core of pathology is attachment disorder, but in other cases core might be aggressive or impulsive behavior.

Bohus - Shame plays key role. Shame plays a very important Role in BPD. If we look at evolutionary aspect of shame – social attractiveness is key and losing it causes shame. Not sure whether it is the major important thing but it is key.

Linehan – is contention that the average BPD has problematic interpersonal relationships – is that genetic or is that just the problem no matter where it came from.

It is probably as heritable as affective instability or impulsivity. What is heritable may be hypersensitivity in interpersonal reactions. Disorganized attachments within the first year – phenotype going back into childhood. Should conceptually take its place along side of affective instability.

Do most attachment people think it's heritable?

Do we want to think narrowly or think about phenotypes as domains? We are in such a different place now than 15 years ago with genetics that to think about what's biological when we know that environment turns genes on and off we would do better to think of affective and impulsivity characteristics.

Bender - my proclivity is to treat patients and come up with ways to treat them so heritability is secondary.

Heritability doesn't make that much of a difference. Treat all three areas as distinct.

Genes don't always get expressed.

Shiner - Developmental research on attachment. The way that people behave interpersonally is heritable and trait related not just attachment related. Studies show little evidence for attachment traits being heritable. Not necessarily continuity between childhood and adulthood attachment styles. Low self esteem, high stress sample showed no continuity and this is a population likely to develop BPD.

Neale - risk factor vs. epiphenomenon. There are statistical models helpful in answering this question. We can disentangle whether A causes B or vice versa. Twin studies are a good place to start but only a beginning. Modeling cause and effect? If one trait is highly genetic you will see high correlation between twins: look across twin across trait and see if the same kind of pattern correlates.

Have to have four intersecting areas to get the disorder diagnosis. In many ways it's a better way of looking at it because it doesn't say which is primary. Any may be primary at any given moment. It might be multifaceted at any time.

Siever – multi factorial thinking. We need to think about how we define the domains and traits because the way you define the traits is going to inform diagnosis. We are talking about different levels and different tools for understanding. We don't really know that much about neural circuits and self identity and attachment etc. Attachment is such a super ordinate paradigm – you could look at heritability of affect but it is so intertwined. Lots going on at biological level that effect affect regulation. What are the components of attachment and how are they disturbed, if we start equating the three categories on a level playing field they are very differently categorized.

Dimensional perspective – in order to be diagnosed in DSM you don't have to be disturbed in all three domains. We may want to say that because of this DSM is no good.

Krueger- need large samples to do this work in the way we are thinking about it. That is crux of challenge. Complex clinical phenotype.

Affective Features Group:

Watson:

Promising start on affective dysfunction in BPD but don't know much. We know about their affective dysregulation but not nature of it. My paper focuses on design and assessment. Mood variability and _____. Important to have clinical and non-clinical control groups. People almost never study men and they show monthly variation. Best design for studying affective dysregulation is experience sampling designs. Time contingent methods or random sampling. To unpack these issues in terms of what comes first – response contingent studies like mood diaries. Take advantage of new millennium technologies. One thing we don't really know in this literature – interpersonal stressors is that their irritability can not be related directly to environment. Importance of measuring affect in a comprehensive way.

Trull:

What are affective features? Major affective features don't distinguish BPD from other disorders. We are finding that elevations on depression and irritability don't distinguish BPD. How can we measure it, how is it currently measured? Sampling methodology using electronic diaries – 50 outpatients, half with BPD other half have dysthymia. Randomly prompted to randomly record mood changes. 168 assessments on each person, on mood state. How do we best measure variability? Briefly – a lot of people take a standard deviation, when we do this we do find BPDs do things that endorse affective instability. Intense, acute changes in affect. Using these D scores that distinguish two groups – negative affect characterizes all but one. Looking at correlations between EMA measures – we see they may not be tapping into this if you look at electronic diaries. Often what they are endorsing does not agree from day to day.

Hooley:

Problems with the DSM – overlooks key feature of BPD. High levels of stable negative affect. Rather important. Analyzing some of the neuroimaging studies. 13 BPD

patients, 10 healthy controls and 10 dysthymia patients. We'd expect that the people with dysthymia have high levels of stable negative affect. Different pattern emerged – BPD and Dysthymia patients BPD looked a whole lot worse in stable negative affect. Higher levels of baseline negative mood. Higher on mood and anxiety and anhedonia. SNAP higher levels of negative temperament. No differences in positive affect. Differences in instability – high for everybody. BPD have higher test retest correlations. Clearly dealing with very large affect sizes. DSM IV underestimates pain and dysphoria that these patients suffer. If this is the case we have a situation where BPD patients are negatively primed.

Linehan:

Basic contention. BPD is a disorder of pervasive emotion dysregulation. Is this the same as affective? Cognitive physiology neurobiology etc. full system response. Dysregulation - can't achieve goals. BPD comes in at different baseline from other PDs. Difference in reactivity also? Not really they start out so high that when they go up it's extreme. BPDs react to different stimuli than other people do. Highly aroused to begin with. Difference in stimuli. Difference in consequences of various emotions – shame is best predictor of suicidal behavior. Anger is predictive of severe interpersonal problems. Shame predicts suicidal but not self injurious behavior in BPDs. We have to look at emotions themselves. We need experimental research. We need to look at mechanisms of action. I think that in treatment research we need to get all treatment researchers together. Need to look at differences in stimuli and effects. Move out of correlation and into experimental. Bring in emotion researchers.

Shiner:

Developmental aspects. Temperament. Think about development in two different ways – 1 BPD traits 2. Adolescent manifestations. Where does condition develop from? Very little is known about etiology of this disorder. Age criterion in diagnostic sense – little developmental research done on this disorder. Traits – all have been identified in young children. Irritability in young children, anxiety and interpersonal aggression. Also attention, regulation all traits that need to be looked at over time. Important to look at development of these traits over time. Look at early traits that children have. Multifinality. Meaning you might have the same end point but arrived at through very different paths. Different developmental pathways to getting to these endpoints. People need to also look at what happens in adolescence. Great issue of development and psychopathology. Manifestations of psychopathology in adolescence – Any discussion of phenotype has to include what it looks like in adolescence. Phenotype is already somewhat in place prior to adulthood and probably peak in adolescence.

Shea:

Comorbidity. 1. Term comorbidity originated with a different meaning – distinct co occurring diseases or entities. We don't have that... we use our descriptive constellations of signs and symptoms assuming categorical entities that don't exist in that fashion. Rather than thinking of comorbidity think about co occurring abnormalities on these dimensions. Three basic dimensions – that's where we want to start where does overlap with other disorders start? Rather than true comorbidity one problem or disorder can put

one at risk for other disorders. What is artifactual? Is there something distinct about these three dimensions? You can have abnormalities in two of the dimensions and not have BPD. Is there something unique about this constellation of abnormalities on the three dimensions? Relationships among dimensions – functional? Shared etiology? Affective instability: does BPD have its distinct area as currently defined? Are there only spectrum disorders? How do they interact is important. Recommendations: Interpersonal stuff as played out in adulthood as a consequence of mood. Experimental designs. We should find something unique about BPD this way.

McNally:

Free association: notice systematic bias in current clinical state vs. past event. Report it differently. Emotion dysregulation reminds me of neuroscience work on fMRI – monitor prefrontal and cortical processing while people are experiencing emotions. Shame and humiliation and rage and anger. Rebecca referred to resilient kids, which reminds me of some of this recent research. People are trying to use genotypical research – maybe we should use it. Lastly, self-representation and biases and schema: very rich literature on anxiety disorders and self-representation. Some possibilities to exploit cognitive psychology for BPD diagnosis.

Comments/Questions:

Anger. Anger in BPDs is a protective response masking shame and sadness.

Trull – palm pilot research gets compliance of 98% and patients like it. Say they have learned a lot about themselves. 3-5 minutes to record patients' mood each time. Can do very intensive studies over a day or two. Self monitoring effect causes mood to stay the same and decline in negative affect. So, there is not self monitoring component.

Defining Affective vs. Emotion: heterogeneity between the two and we need to get a consensus. Maybe this can develop from the afternoon group session.

Shea – think about it hierarchically. General tendency toward negative emotions but they can be more fine grained distinctions. They co-vary but you can still distinguish them.

Hooley – People with BPD react to different stimuli than other people do. BPDs look unreactive if you look at Central Nervous System, but in fMRIs you are using subtraction paradigms. So, the ceiling effect is at work in the brain but not in the physiology.

Linehan - Emotion regulation and dysregulation are two hot topics. Trying to define and figure out what we mean – within BPD in particular you have very high efforts to regulate _____... A large part of what parents do with kids is teach them how to regulate their behavior. Is the problem with BPDs that they didn't get proper amount of this or that they required more than others? From a developmental point of view watching how parents react to dysregulated children – effect of one on the other would be useful. My theory is a transactional theory.

BPDs use more dorsal lateral areas. So they are using more of the centers that we would use.

Shea - Is high reactivity general to any PD or is it specific to BPDs? Will specific stimuli trigger that affect shift?

Increased level of intensity and frequency with any emotions in BPDs. Any emotions – even positive emotions.

Shea - Is the TRIGGER for BPDs specific?

Morey - Disconnect between retrospective. Cognitive studies of memory – BPDs remember the negative words. Had huge negative bias. Tremendous sensitivity to negative stimuli.

Siever - You can look at responses to positive stimuli and subtract it from negative stimuli – if you look at responses across the board you find that BPDs are more sensitive to negative stimuli.

Livesley - We seem to be identifying a general hypersensitivity. And I think there is a general hypersensitivity that intensifies.

Impulsive Features Group:

Verheul:

We start from a heterogeneous construct and try to decompose it from heterogeneous components. I like the question of what kind of stimuli are connected to affective disorder. Disregulation is too general – it a fuzzy concept. There are a variety of other behaviors like risk taking etc. that are particular to BPD. A study I liked used the 5 feature model and found traits used to alleviate negative self regard: 1. urgency 2. lack of perseverance associated with self discipline. Impulsivity is a combination of different things and urgency explains most of them. It accounted for 50 – 60% of variance in BPD scale. Urgency is really at the intersection of impulsivity and _____... Get rid of Impulsivity and use urgency and link it to hypersensitivity otherwise we will find that almost all patients with a PD have BPD.

Links:

1. When we study impulsivity we have to be in parallel studying affect. It seems to be a hallmark of the disorder and the interplay of the two will take us forward. We found that all patients endorsed having affective instability, but from one to the next it's very different. Some have high negative mood some have high negative mood and variability.

2. Things to learn from treatment studies. Anger and impulsivity respond to medication. Much more so than depressive affective. We would like to have an agency that would fund this kind of research.
3. Don't forget suicidal behavior in BPDs, it's an important phenotype of this disorder. It's clinically salient and it can tell us a lot if we look at people who've committed suicide.

Coccaro:

Impulsivity and aggression are not really synonymous. 25% of borderlines have enough aggression to be diagnosed with IED. We have to ask where we are getting our BPD samples – treatment seeking BPDs are different from volunteers etc. We did something unique- looked at twin studies. You can do it in two ways – psychometrically or behaviorally. Honduri conceptualized behavioral impulsivity as heritable and response dependent. When you actually look at what distinguishes BPDs you see they ARE more impulsive and more aggressive.

Siever:

One recommendation coming out of early advisory committee: take particular measures for endophenotypes and test for variability and partition out components. Behavioral phenotype is going to vary. We have looked at over 300 people now to get a valid endophenotype. BPD is an emergent phenomenon and emerges as a valid phenomenon over time. When you get to genes you get more specific genetically b/c there is no specific gene for BPD. For our psychometric tests – they all factor together in a unitary factor. By using measures based on constructs related to BPDs we found test retest reliability and that most tests did differentiate the BPDs from other PDs in the control. If you are going to look at gene expression etc. there is value to identifying specific endophenotypes.

Clark:

SNAP assessment corresponds with interview .75. No clear thresholds for distinguishing patients cross PDs. 93 ways to met diagnosis if you require 5 of 8 criteria. 40 patterns had 5 or fewer patients each. Many instances in which two people were diagnosed with BPD and shared single criteria. Figure 4 shows that BPDs get more and more disturbed as they have more characteristics. Fig. 7 both groups diagnosed BPD but only overlap in 2 features... what is the diagnosis buying us? Which would be more clinically useful fig. 7 or fig 8.

Waldman:

Twin and adoption studies show high heritability for ADHD. After some promising leads – after initial positive findings there were substantial failures for replication. Find endophenotypes that are more suggestive of the disorder than those that manifest the disorder itself. One of the problems is that a field can get hung up on particular measures. I pulled together criteria for validity for molecular genetic studies. Key points or challenges with studying endophenotypes vs. symptom dimensions. Be clear about constructs and their measures. Some criteria for endophenotypes are easier to satisfy than others. Higher threshold would be to show common genetic influences with the disorder

itself. It's a useful idea to look at endophenotypes, but at the end of the day you have to build back up to the disorder itself. If one goes and finds genes for specific traits. One still has to go back and build up to the disorder itself.

Comments/Questions:

Term impulsivity refers to so many different types and facets of behaviors. We need to figure out what characteristics of impulsivity are specific to BPD.

Paris – to have BPD defined by 5 of 9 criteria is crazy. How did this happen? (it's more than half)... It's an arbitrary decision. If you choose 6 or 7 you get much more differentiation. Now we know much more about the essential features of the disorder. DSM definition of BPD is useless. We could fix the categorical and make it much better.

If you read through the criteria very well it lays out specific features – the central features are in the text but not on the list. It's a layout question not a content question.

Database comment: we have a paper coming out in comp psych in which we did an interpersonal relationships and latent class analysis of BPD. In latent class analysis – only two classes and threshold is three criteria.

Westen - when you look at all three constructs, you can say it definitionally or empirically. Look at list of items and refine over time, identify items that could be used as criteria. It's same procedure of construct elevation. See what they predict in terms of outcome. Second issue – that all assumes that you are looking at a single population and assuming you don't have subtypes. When we look at adolescent adult data – internalizing subsets are less extroverted vs. angry impulsive types.

Bohus - Impulsivity in BPDs is strongly correlated to ADHD. This may be a subtype of BPD.

“Emotionally dysregulated BPD subtype”

Gunderson - Arguing need to define our constructs. One misused construct is impulsivity it clearly refers to a range of behaviors. It is probably linked to affect regulation. Etiologically doing things on a whim is a huge spectrum and that's what this refers to. BPDs are high on self harm, recklessness and sensation seeking. We have to be much more precise if we are going to tease things out.

Morey - Comorbidity got worse as you increase the number of criteria. This doesn't work. When you go into community samples the gender differences for impulsivity change.

Big difference between impulsive aggression and impulsivity.

Siever - Lots of the scales that we use were not developed specifically for BPDs. There are BPD scales that include impulsivity but the scales for impulsivity were not designed for BPDs. We found that all scales distinguish BPDs and discriminate the three groups. If you're talking about precision for defining constructs broad ones do distinguish.

biological measures; what components are you correlating?

If you look at avoidant and schizotypal BPDs they have high severity of pathology. You can't factor out any one variable enough to say that we have a single construct that accounts for all self report differences.

Negative affect accounts for all these other constructs.

Linehan - Always thought of impulsivity as a function of negative affect, but research I do always selects BPD plus one other key dysfunction. The importance of this particular issue has come up a lot. I have populations that never get better no matter what you do. Whereas, Mary's population had improved. Almost everyone I treat has 6-7 criteria. We need to look at levels of BPD – spectrum. We don't totally understand how a person gets in control. In absence of emotional arousal are there standards of impulsivity?

Siever - I would wonder about people who are sociopathic but don't have intense affect. Whereas BPDs are mostly characterized by intensity of affect. If you give BPDs tests that don't elicit intense response you still have high scores from BPDs.

Shea - Do we want to say that you have to have representation on three dimensions?

Cross – Cutting Features Group:

Sanislow:

Cognitive features of BPD phenotype. Cog. Features cut across broad range of areas – varieties of impulsivity as well as having relevance for relationships. There is some real value to using experimental approaches when you think of cog features to BPD. In particular I want to make a case for looking at cognitive reappraisal or those kind of broad based top down things that might be familiar in clinical practice, but I want to make the case for looking at more basic level of disruptions of cognitive processes. The kinds of things that happen on an order of milliseconds, things that relate to the kinds of things we're going to study here. And so, there are a couple of principles that I think it's important to adhere to. One of the things is that we should be looking at the different basic processes. For instance, if we talk about looking at attention; attention can involve different things we can look at earlier or later attention processes and where disruption in attention may occur may have relevance for BPD. Same thing when we talk about working memory. Working memory is made up of a lot of different components and processes that go into it. We have to update and retrieve information and these things are important in how a patient processes emotional stimulation. If we decompose those paths into isolated events we might see specific disruptions that we might not see or that might explain results that are contradictory when we look at a broader process like working

memory. Part of the emphasis we can look at is cognitive emotional interaction. Maybe BPDs are more in tune to negative stimulation or that over time they may evaluate things as more negative. I would also suggest that we look at processing that doesn't include emotion. There may just be difficulty with resolving conflict when presented with two competing stimuli even when the content is not emotional. Caveat: This is really experimental work at this stage. Highly dependent on what type of the phenotype we decide to focus on. Not going to give us magic bullet assessment thing. We can't say that we know that emotional processes are interrupted in BPD patients. We are really investigating at this point.

Bohus:

Pain processing and dissociation – There's no doubt that some of fundamental new biological mechanisms that affect BPD patients. We have now a series of morphological and MRT studies. It's important that we have at least 5-6 different areas: We have prefrontal disinhibition, amygdala hyperactivity, problems in the ACC and problems in the hippocampus and Cummins. On the one side, strong impact on development of BPD and on the other hand on emotional learning development and learning process. And we correlate this with amygdala and hippocampus activation. And what we really find is a learning disability. So, concerning pain we found in the last five years we found that concerning pain, reduced pain perception might be both a marker for genetic susceptibility and a marker for the current levels of stress. This is first based on the clinical experience of any patient that is applying self-injurious behavior that she's doing that in order to reduce stress. 70% of those patients who are mutilating themselves report hypo _____? during self injurious behavior. So the first thing we did was called pressure tests and found that pain perception is negatively correlated with stress and positively correlated with this distinguishing feature. And we could both show that even under non stress conditions BPD patients show increased pain perception and this clearly distinguishes them from patients with depression and patients with anxiety disorders– it is unique to the Borderline patient. The question is whether this pain perception has something to do with diminished somatosensory pathways could be ruled out. We eventually correlated potentials and what we find is that not only are pathways ok, but that they are hypersensitive to pain on somatosensory cortex. But if we put them in FMRI, FMRI will show an increase activity in the post lateral prefrontal cortex and a strong decrease at the Anterior Cingulate. Anterior Cingulate has a lot to do with affective motivation and with self-referential processes. And to our surprise, the amygdala _____ when they were confronted with pain. Next step is imaging genomics (?). Doing the twin studies is one thing, but if we want to have experimental designs, with the FMRI it's really easy to look at the genes. You need small numbers of 20-25 non-medicated patients and you have to very clearly access to functional levels of their brain. What we found were strong correlations between the dysfunctional pain perception and the CUMT fissure (?) in borderline patients. This is not surprising but it's the first idea on that. We can look for subtype discrimination but we did not investigate patients who experience normal pain perception; the second thing is we are currently following susceptibility to treatment whether it's a trait on the _____ level and we're looking for neurobiological underlyings..

Krueger:

Expanding structural model of Psychopathology. I was assigned the task of explaining BPD from the perspective of internalizing and externalizing. When we first began to collect data on cognitive processes in the general population we found that they don't come in clear groupings, which might be suggested by something like the DSM. Because of this kind of pattern in the data it became necessary to develop some model of understanding to figure out how to work with these kinds of data. One perspective involves diagramming internalizing another is substance use and excesses of the personality described as externalizing. There are a number of things we discovered about the way these spectrum concepts work. For example they tend to be genetically coherent. We've also pursued statistical modeling studies that show these disorders don't define categories in general population samples. So when you fit them all into characterizing something as categorical and you compare them directly to a model that characterizes them as elements of dimensions - the dimensional model actually fits the data better. The dimensional model characterizes symptoms of in the process we converged on a model of common mental disorders. Being assigned this topic opened up an opportunity to find out how the Borderline phenomenon might intersect with this model. Generally speaking BPD has not been studied in these kinds of epidemiological samples. So the fact that it's changing caused us to go out and look for data that we could use to try and understand how Borderline symptoms fit into these internalizing and externalizing things. We got some data from the office of Medical Statistics in Great Britain - a large epidemiological sample of over 8,000 participants who were categorized in terms of the usual axis one kinds of conditions. They also completed the entire skid screener and this allowed us to look at empirical structure of all of the varieties of psychopathology at the same time. So they broke these data down into a number of distinct variables that represent variables that represent criteria for conditions that we'd studied previously, but also axis two criteria and did a very exploratory analysis to see if three were underlying dimensions that could be explain the way the symptoms tended to appear in different groupings. What we found was that BPD criteria are very complex and are associated with multiple dimensions of variation. The perspective that's emerged from that work is very compatible with what people have said here today and very compatible with my clinical experience. And supports the idea that BPD is actually a confluence of separate dimensions and that that way of thinking about it is helpful. We've worked on Psychopathy in the same way. We find that it's similar in that it combines separable dimensions into coherent clinical concepts. Part of what goes on with clinical personality concepts is that they really reflect a confluence of separate dimensions, which are particularly problematic for people to deal with but salient in our clinical studies.

Livesley:

BPD from a Genetic perspective. Want to preface my statements by saying that in addition to perspectives we've adopted we might want to think about a bottom up approach. There's a good case to be made for complimenting these perspectives with a bottom up approach by looking at how characteristics naturally cluster in different sample. As part of that we can incorporate them in a systematic way and habituate a strategy where we set up model to be tested in an organized way. Given that, the second point is that we can conceptualize them as consisting of a core pathology involving the

failure to establish a coherent understanding of self and coherent concept of representation of others or alternatively chronic interpersonal dysfunction involving failures of attachment or intimacy. Plus emotional dysregulation are clustered traits. The third point I want to make is that genetic information can be useful in delineating and refining that phenotype. Currently, molecular genetics not particularly useful here for taxonomic purposes. It does look as if Behavioral genetic information can provide additional source of information within the context of a construct validation framework. I'm suggesting that behavioral genetic perspective might be useful because, first of all it looks as if most of the characteristics for BPD might be heritable and secondly it looks as if BPD corresponds closely with underlying genetic architecture. The fourth point is we'd like to emphasize the importance of developing an account of primary trait structure. Primary traits I'm seeing as the basic unit of explanation and description. That's the level of analysis that's probably most pertinent to behavioral and biological analysis of clinical intervention. Fifthly, the most effective way of proceeding is to use a construct validation framework. As we think of this model we begin by developing theoretical definition of disorder that's as broad as possible and then confirm that structure by using phenotypic and genetic analyses modifying it as necessary and once we confirm that, then decompose the primary traits into their different components preferably using a behavioral genetic approach and then finally reconfirming the structure into external validity. When we apply that we come up with a phenotype of BPD that I describe on page 173. There is a list of traits organized primarily by affective traits. High level of anxiousness, affective lability that decomposes into a reactivity component and an intensity component both of which are modulated by a hypersensitivity component. And the trait that I'm currently working on, which I call for want of a better term, is anhedonia, which is this pervasive negative affect that we've been talking about. And there are a couple of interpersonal traits like insecure attachment, submissiveness and that's the sort of package that categorizes BPD.

Zanarini:

Longitudinal Studies. As I've mentioned before, my work in studying BPD has lead me to believe in a multifaceted phenotype that has affective, cognitive behavioral and interpersonal features. We have ten years of completed data; we looked at symptom resolution and defined two types of symptoms acute and temperamental. Acute symptoms that are akin to positive symptoms of schizophrenia dissolve relatively rapidly and are specific to BPD. Also defined temperamental symptoms that are some of the negative symptoms of schizophrenia. They dissolve relatively slowly; they're not specific to BPD and in my way of thinking are strongly associated with psychosocial impairment. We did analysis on this 10n year data. We studied 24 symptoms of BPD and found that about 12 were acute in nature and 12 were temperamental in nature. And they grouped not just by time but by nature as well. And basically the impulsive behaviors that are specific to BPD such as self mutilation and help seeking suicidality were acute in nature as were the interpersonal symptoms indicating a struggle to get well. Symptoms of protest in activity and assertion. And the temperamental symptoms tended to be chronic affects as well as the softer more interpersonal problems such as problems with dependency and abandonment concerns. The symptoms we are most concerned with resolved most quickly and symptoms we were not as concerned with are more stable.

And I think this has implications for our methodology. I think we should structure the criteria in 4 sectors and while I think DSM V should mention the acute symptoms but that if only the acute symptoms were put in you'd have a disorder relatively quick to resolve; a very colorful disorder and if only the temperamental symptoms were put in you'd have a more chronic disorder. In terms of research we really need to look at the course of some of these things. We should match what we see clinically and repeat studies over time. Critically important to study BPD in children. I think it's critical to look at role of temperament as well as adversity going forward.

Neale:

Statistical Models: Empirical question – how substantive are individual differences as quantitative or qualitative? Our group has been collaborating with people in Norway looking at BPD symptoms in twins amongst all the other personality disorders. One of the fundamental things in psychometrics the idea of measurement in variance seems somewhat underutilized. The dimensional model can certainly be compared for its fit against the fast time model. And it was mentioned earlier the dimensional model seems to be a little bit better. It has other utilities because there are certain predictions you would make – if you've got some factor and it changed then all of the symptoms should change proportionately to their relationship to the factor. There are applications of the genotype is a very useful lever; twin studies mentioned the idea of teasing apart different models of comorbidity (co mobility?) In fact, there are very few variables that I really trust as exogenous, so called independent variables: I trust sex and age and genotype. They are really useful as things that will not be affected by whatever you do. We need developmentally informative studies. And ideally both at the same time. If you could get symptoms of BPD repeatedly measured over time in a genetic framework we'd come up with genuine differences in mobility as well as differences in tonic levels.

Comments/Questions:

Chuck was saying that Cognitive work is helpful with BPD, and it's often useful to distinguish between cognitive deficits and cognitive biases.

Linehan - I start out with the absolutely most severe patients. Suicidal BPDs stay suicidal for a long time. We get people who come back into therapy and still don't meet the criteria for BPD, but they are still more sensitive to certain kinds of feedback than clients who have never met the criteria for BPD. It makes me think that we really ought to be looking experimentally into this sensitivity that may already be there with this particular group of people.

Sanislow - This is just investigation: Are you suggesting that hypersensitivity becomes more pronounced during the course of treatment or was it already there?

Linehan - Take the construct of validation: many of my patients are exquisitely sensitive to invalidation. But, 20 years later when they come back for something minor – they are not unhappy, but right away if there's invalidation of core beliefs about the self, arousal

goes up, cognitive processing goes down. You can immediately get rid of it by validating them.

Paris - Just to contextualize, the Outcome data that _____ came up with found that BPD is a mixture of temperaments and symptoms. The symptoms resolved and the patients seemed to be cured. Given that that is the case, what are the implications for the phenotype of the disorder? You suggested that we can separate the acute and chronic symptoms, but how do we do that, what are the implications?

Zanarini - What we found is that among admitted BPD patients there are subtypes and I haven't fully analyzed the data but there seems to be a type that didn't have a lot of what I would call temperamental symptoms they also did not have a comorbid dependent or avoidant personality disorder at baseline. And those people go on to achieve the normal milestones of adult life. But people who I call, for lack of a better phrase, early-retired people have a tremendous amount of shyness and avoidance and it's much harder for them to go on with their lives.

Morey - I think the maturation process diminishes some BPD traits. With regard to Joel's questions about classification – Disregulation and impulsivity diminish, as people get older. Maturation process impacts some of these traits and starts to diminish disorder into middle age.

Linehan - Big difference between someone who is still symptomatic and what I'm talking about. Relational self is a self that is defined by the context that you're in. Autonomous self – no matter where you are the self is still there. The point I'm making is that people who meet the criteria for BPD have a characteristic that once the flagrant stuff is gone they have great lives but if you put them in a different situation, one that's antagonistic to what I'll call The Relational self – There is a contextual component to this disorder that in the appropriate context these people have no problems, but put them in a context that challenges the self identity and they present as BPD. Accounts for adult onset BPD.

Interpersonal processes govern the symptoms of BPD. Traits that distinguish BPD are the more florid symptoms – for DSM V it might be good to include things that are descriptive of disorder but not distinctive and are activated by stress.

Livesley - It seems as we talk about this we are talking about three different domains – the symptomatic, the trait, and the self interpersonal and this touches upon what we mean by personality disorder, but if we come from a trait dimensional perspective it's possible for people to have emotional dysregulation – high levels- traits if you like that cluster but don't have a personality disorder. The two may get confused.

Krueger - It may be helpful to think about treatment guidance in terms of separating traits from symptoms. Eg. High stimulus reactivity; some traits can be successfully altered over time, some cannot. There are things that we might put in the trait category that are part of innate personality and will not change.

Paul - The more we differentiate traits from symptoms and then think about how to individually structure treatment plans. Some traits can be altered successfully over time. We are having a parallel discussion about methodology. Approaches that are going to move the field forward because they have funding etc. should be discussed.

Neale - One of the statistical frameworks that might be useful here is a dynamic system models. Describes how quickly patient returns back to the level. One question is how quickly you turn the corner and the other is how quickly you come back to the level. It seems to me that certain temperaments generate certain types of behaviors. So the idea of someone who is absolutely furious one moment and happy and chatting calmly the next one is consistent with a _____ model. So I'd like to see a bit more application of the dynamic systems model.

Sanislow - when I hear talk about traits and symptoms, it brings to mind past discussions about where we draw the line between axis one and axis two disorders. That should be infused and part of some of our considerations. There are conceptual reasons for thinking about where that boundary should be.

Clark - What about Personality disorder as a disorder on axis one and define the disorder on axis 2 ? Possible solution.

Discussion of Groups' Task:

Core features
Current measures
Standard measures
Evaluate standards
Future research agenda in this area

Can we begin thinking about genetic studies – molecular biology? Is there a core of people who 90% of you in this room would agree is borderline and start with molecular genetics there or is it too early?

We might all agree that they were BPD but we would disagree on how we would characterize them.

It might not be easy to find a set of genes that define this disorder but we do have some phenotypes for some of the traits of BPD.

Stage of phenotyping suggests that we are not quite ready to begin genotyping.

Any optimism about pharmacological treatment?

Collect blood samples now and look at it in the future. Many of us measure exceptionally well what is going on with BPD and if we had a way of collecting samples now it would be pertinent 10 years from now and we need a storage.

If we combine fMRI with genetics.

Paris - all psychopharmacology that we apply to this disease were developed for other diseases. We should go the route of basic research and then build the psychopharmacology from that.

Zanarini - these drugs take the edge off, but none of them treats the disease.

Waldman - pursue two complementary strategies? Get BPD researchers to look at genetics and agree on diagnosis. High severity and complimentary nature of this disorder.

Siever - we rarely see full remission in schizophrenia. We have core group of patients and we know something about the treatment – use neuroimaging and translate it into prediction of treatment response. We have to use genotyping, family strategies.

Estimated incidence of BPD = little over 1%. Similar to Schizophrenia.

Linehan: National Alliance for the Mentally Ill did not consider BPD as a mental disorder because it does not have a biological component. Also people don't like them. They have finally put them in NAMI and Marsha is going to speak with them. BPDs have high risk for suicide attempt and everything else. So, people are afraid to do research with such a high risk group. Getting young people into it is difficult – most suicide research is done in Europe.

Remainder of day, participants completed their task in the four working groups.