Longitudinal Psychiatric Symptoms Progress in Prodromal Huntington Disease: a Decade of Data

Eric A. Epping, MD, PhD[1], **Ji-In Kim, PhD**[1], **David Craufurd, MB, BS**[2], **Thomas M. Brashers-Krug, MD, PhD**[1], **Karen E. Anderson, MD**[3,4,5], **Elizabeth McCusker, MB, BS, FRACP**[6], **Jolene Luther, BA**[1], **Jeffrey D. Long, PhD**[1,7], **Jane S. Paulsen, PhD**[1,8,9,*], and **the PREDICT-HD Investigators and Coordinators of the Huntington Study Group**

[1]Department of Psychiatry, Carver College of Medicine, The University of Iowa, Iowa City, IA, USA

[2]Institute of Human Development, The University of Manchester, Manchester, England, UK

[3]Huntington Disease Care, Education, and Research Center, MedStar Georgetown University Hospital, Washington, DC, USA

[4]Department of Psychiatry, MedStar Georgetown University Hospital, Washington, DC, USA

[5]Department of Neurology, MedStar Georgetown University Hospital, Washington, DC, USA

[6]Department of Neurology, Westmead Hospital, The University of Sydney, Sydney, New South Wales, Australia

[7]Department of Biostatistics, College of Public Health, The University of Iowa, Iowa City, IA, USA

[8]Department of Neurology, Carver College of Medicine, The University of Iowa, Iowa City, IA, USA

[9]Department of Psychology, The University of Iowa, Iowa City, IA, USA

Abstract

Objective—Psychiatric symptoms are a significant aspect of Huntington disease (HD), an inherited neurodegenerative illness. The presentation of these symptoms is highly variable in patients, and their course does not fully correlate with motor or cognitive disease progression. We sought to better understand the development and longitudinal course of psychiatric manifestations

[*]Correspondence to Jane S. Paulsen, The University of Iowa Roy J. and Lucille A. Carver College of Medicine, Psychiatry Research, 1–305 Medical Education Building, Iowa City, IA USA 52242-1000. Tele: 319-353-4551; Fax: 319-353-3003; predict-publications@uiowa.edu.

in patients who carry the HD mutation starting from the prodromal period prior to motor diagnosis.

Method—Longitudinal measures for up to 10 years of psychiatric symptoms from the Symptom Checklist-90-Revised were obtained from 1305 participants (1007 carrying the HD mutation) and 1235 companions enrolled in the Neurobiological Predictors of Huntington's Disease (PREDICT-HD) study. Participants with the HD mutation were stratified into three groups according to probability of motor diagnosis within five years. Using linear mixed effects regression models, differences in psychiatric symptoms at baseline and over time between HD mutation positive groups and controls were compared as well as between HD mutation participants and their companions.

Results—19 of 24 psychiatric measures showed significant increases at baseline and longitudinally in HD mutation carrying individuals or their companions versus controls. The differences were greatest when comparing symptom reports from companions (versus self-report), especially in participants who were closest to motor diagnosis.

Conclusions—Results indicate psychiatric manifestations develop more often than previously thought in the HD prodrome. Symptoms also increase with progression of disease severity. Companions of HD mutation carriers also report greater psychiatric symptoms over time compared to affected individuals, consistent with decreasing awareness.

Introduction

Huntington disease is an autosomal dominant neurodegenerative disease that typically manifests in adulthood with motor, cognitive and psychiatric symptoms. The disease occurs due to an expanded number of cytosine-adenine-guanine (CAG) trinucleotide repeats in the protein-coding DNA sequence of the Huntingtin gene on chromosome 4. A formal diagnosis of Huntington disease is usually given based on the presence of significant motor symptoms, including chorea, rigidity, and bradykinesia. Huntington disease is progressive over several years, leading to functional decline and premature death (1, 2). Cognitive changes include progressive deficits in learning, executive and sensory functions and attention, resulting in dementia (3–6). Psychiatric manifestations in Huntington disease include depression, irritability, apathy, perseverations, obsessions, and occasionally psychosis (7–14). With a few exceptions (7, 15), psychiatric changes are not typically related to indices of progression.

The neurodegeneration of striatal and cortical structures underlying the symptomatic presentation of Huntington disease has been known for some time, and while there is an association between the number of CAG repeats and age of onset, there is significant unexplained variability in the presentation and severity of symptoms, in particular its psychiatric manifestations. The ability to test for the Huntington disease mutation prior to onset of symptoms, known as the illness prodrome, has provided the opportunity to study the development of disease manifestations over time. The longitudinal Neurobiological Predictors of Huntington's Disease study (PREDICT-HD) has identified motor, cognitive, psychiatric, and brain imaging changes that occur in individuals with the Huntington disease mutation (16–19). We reported an increase of psychiatric syndromes for individuals in the

prodrome of Huntington disease at the time of study entry, and we have shown increases in symptoms cross-sectionally as estimated proximity to motor diagnosis nears (4, 19–21).

Here we report longitudinal psychiatric ratings from up to ten years of PREDICT-Huntington disease follow-up in order to better characterize psychiatric symptoms that occur in the Huntington disease prodrome up to and through motor conversion. We have also developed statistical models to evaluate whether there are differences in the trajectories of psychiatric manifestations as reported by participants versus companions, which has implications for psychiatric assessment in Huntington disease and other disorders where changes in awareness are prominent (4, 22).

Method

Participants

Participants were from the PREDICT-HD study at 33 sites in six countries (USA, Canada, Germany, Australia, Spain, and UK). Eligible participants had to have independently underwent testing for the Huntington disease gene mutation and knew their gene status prior to study participation. That is, independent from study enrollment, every participant was aware of their family history and gene mutation status for HD. The study did not enroll participants who were at-risk but had not undergone predictive testing for the HD gene mutation. Recruitment efforts included the following: talks at regional, national and international Huntington disease lay meetings, flyer dissemination to genetic counseling and Huntington disease clinics, development of a PREDICT-HD website and links to/from other Huntington disease sites. Individuals with the CAG repeat expansion (CAG 36) (23, 24) served as cases while those who tested negative for the gene expansion (CAG<36) served as controls. All were 18 years of age or older and not diagnosed with manifest Huntington disease at study entry. Exclusion criteria included unstable medical or psychiatric illness, active substance abuse, history of a significant developmental cognitive disorder, significant history of head trauma or other central nervous system disease, the presence of a pacemaker or other metallic implants, use of antipsychotic medication in the six months before enrollment, or the use of phenothiazine antiemetic medication in the three months before enrollment. Study protocol was approved by each site's respective Institutional Review Board. After complete description of the study to the participants, written informed consent was obtained.

All participants were seen at study sites annually. The analysis used data from 1305 participants with 6112 observations and 1235 companions with 5365 observations. Companions were predominately spouse/partner (74%) followed by friend/neighbor (8%), parent (7%), and sibling (5%), and approximately 75% of companions reported living with the participants. The mean number of years companions reported knowing the participants was 20.77 (SD=13.59) years. The median number of follow-up visits was 5 (range=1–10).

Progression Groups

Individuals entered PREDICT-HD with different genetic exposure according to their CAG repeat lengths and current ages. To yield valid inferences, gene-expanded participants were

classified into three groups based on their CAG-Age Product (CAP) score (25) computed as CAP=(Age at baseline)×(CAG–33.66). The CAG-Age Product formula was derived from a parametric accelerated failure time model predicting motor diagnosis from age at entry, CAG length, and their interaction. CAG-Age Product is similar to the "disease burden" score of Penny et al. (26) and purports to index the cumulative toxicity of mutant huntingtin at the time of study entry. Cutoffs were derived for the best fitting subgroups based on an optimization algorithm using an earlier sample of PREDICT-HD participants (25). Based on gene status and the CAG-Age Product distribution, four groups were defined in this analysis: Control (gene non-expanded), Low, Medium, and High probability of motor diagnosis within five years. The estimated time to motor diagnosis for each CAG-Age Product group is >12.8 years for the Low group, 7.6–12.8 years for the Medium group, and <7.6 years for the High group.

Measures

The Symptom Checklist-90-Revised (SCL-90-R) is a 90-item self-report scale of psychiatric symptomatology with each item rated on a scale of 0=*not at all* to 4=*extremely*, based on the degree of distress over the previous seven days (27). Three global measures of psychiatric symptoms and scores for nine specific symptom domains are produced from the scale: GSI=Global Severity Index; PST=Positive Symptom Total; PSDI=Positive Symptom Distress Index; SOM=Somatization; O-C=Obsessive–Compulsive; I-S=Interpersonal Sensitivity; DEP=Depression; ANX=Anxiety; HOS=Hostility; PHOB=Phobic Anxiety; PAR=Paranoid Ideation; and PSY=Psychoticism. For all participants, the SCL-90-R was administered by a trained staff member. The PREDICT-HD protocol requested annual exams including standardized cognitive, motor, functional and psychiatric ratings as well as brain scans.

Statistical Methods

Baseline characteristics were compared by group using an analysis of variance (ANOVA) for continuous variables and a chi-square test for categorical variables. All tests were two-tailed tests.

Group comparison of baseline and longitudinal change—To examine potential differences between the controls and each of the gene expanded groups at baseline and over time, participant and companion ratings were analyzed separately using linear mixed-effects regression (28). The time metric was duration, defined as the time since study entry expressed in years. All models included sex, years of education, and age at entry as covariates. Three linear mixed-effects regression models were fitted for each outcome variable: no effect, baseline differences only, and baseline and longitudinal differences among groups. The models were evaluated using Akaike's information criterion (AIC), corrected for small-sample bias (AICc). The effect sizes were the *t*-values of either the intercept (baseline difference) or slope difference (longitudinal change) among groups, each computed as the difference of the sample estimates divided by its standard error. Detail of all statistical analyses are provided in the supplemental data.

Participant and companion comparison—To test whether there were longitudinal differences between participant and companion ratings in each group, participant and companion ratings were modeled simultaneously using multiresponse linear mixed-effects regression. All models included sex, years of education, and age at entry as covariates. The models were assessed by AICc values, as described above, to examine which groups had statistically reliable slope differences. The relative importance of the longitudinal change discrepancy of each group was assessed by the sum of the weights (wAICc) across all models with unequal group slopes, as described by Burnham and Anderson (29). A sum closer to 1 indicates higher importance. Model parameters were averaged over all the candidate models after multiplying the weight of the model and the estimated parameters for the given model. Using these model-averaged parameters over all models, fitted curves for participant and companion ratings were drawn as described by Burnham and Anderson (29).

Results

Baseline and Longitudinal Change in Self and Companion-Reported SCL-90-R

Participant characteristics at study entry are presented in Table 1. As expected there were significant age differences between the prodromal Huntington disease groups with increasing age associated with increasing proximity to estimated motor diagnosis. Of the 24 psychiatric outcome variables examined, 19 showed significant baseline and longitudinal differences between prodromal Huntington disease and the healthy controls (eight participant ratings: Global Severity Index, Positive Symptom Total, Positive Symptom Distress Index, Obsessive–Compulsive, Interpersonal Sensitivity, Depression, Hostility, and Phobic Anxiety; 11 companion ratings: Global Severity Index, Positive Symptom Total, Positive Symptom Distress Index, Somatization, Obsessive–Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, and Psychoticism). Three participant ratings (Anxiety, Paranoid Ideation, Psychoticism) and one companion rating (Paranoid Ideation) showed only baseline differences between the prodromal Huntington disease cases and the healthy controls (i.e., no longitudinal differences). Please see Table 2.

Table 3 shows the comparison of each prodromal group (Low, Medium and High probability of motor diagnosis within five years) compared with the healthy controls on each baseline and longitudinal psychiatric outcome. As shown in the top of the table, 11 of the 12 participant psychiatric variables and 12 of the 12 companion psychiatric variables showed significant differences between the healthy controls and the prodromal Huntington disease groups with Medium and High probabilities of diagnosis. In the prodromal Huntington disease group with a lower probability of motor diagnosis, nine of the 12 participant-rated psychiatric variables and only one of the companion-rated psychiatric outcomes were significantly different than the healthy controls. When the groups were compared longitudinally, findings showed companion-rated psychiatric outcomes showed significant change for 11 of the 12 outcomes for the High group, six of the 12 outcomes for the Medium group, and two of the 12 variables for the Low group. Prodromal Huntington disease participant-reported psychiatric symptoms showed significant change over time on seven of the 12 variables for the High group. None of the participant-rated variables showed significant change over time for the Medium or Low prodromal Huntington disease groups.

Comparisons Between Participant and Companion Ratings

A multi-response linear mixed-effects regression analysis was performed to examine whether the differences in longitudinal change among participants and companions were statistically reliable. When the importance of the longitudinal change discrepancy between participants and companions was compared across CAG-Age Product groups for each measure as shown in the Table 4, differences (weight>0.7) were observed for seven measures: Global Severity Index, Positive Symptom Total, Obsessive–Compulsive, Depression, Anxiety, Phobic Anxiety, and Paranoid Ideation. For all the seven measures, the High group had relatively high importance with weights of 0.75 and above. The Medium group had relatively high importance only for Positive Symptom Total and Obsessive–Compulsive. The Low group did not have relatively high importance for any measure. For these seven measures – Global Severity Index, Positive Symptom Total, Obsessive–Compulsive, Depression, Anxiety, Phobic Anxiety, and Paranoid Ideation – fitted curves are displayed in Figure 1 using model-averaged coefficients across all possible models. For the other five measures which did not have groups with longitudinal change discrepancies – Positive Symptom Distress Index, Somatization, Interpersonal Sensitivity, Hostility and Psychoticism – fitted curves are displayed in the supplemental data (Figure SF1).

Discussion

To our knowledge, this is the largest longitudinal study of psychiatric manifestations in prodromal Huntington disease published. Some previous research has suggested that severity of psychiatric and/or behavioral manifestations of HD are not associated with progression of the disease (2, 30). Contrary to this popularly held belief, 19 of 24 measures examined showed cross-sectional and longitudinal differences between prodromal Huntington disease and gene-mutation negative controls. Of the remaining five measures analyzed, three also showed elevated baseline scores although change over time did not differ. Although previous research has consistently emphasized the clinical importance of the psychiatric symptoms associated with Huntington disease, and a wealth of studies have noted the higher prevalence of psychiatric symptoms and increased psychiatric distress in Huntington disease, few studies have documented longitudinal progression of the psychiatric disturbances in Huntington disease. These findings are consistent with Craufurd and colleagues (7) who provide longitudinal data for 111 persons with a diagnosis of Huntington disease, finding that all three subscales of the Problem Behaviors Assessment for Huntington's Disease (PBA-HD) showed significant change over time. Further, Craufurd (7) showed whereas all three psychiatric subscales (Apathy, Irritability, Depression) worsened over time in the earliest stages of Huntington disease (Stage I and II), only Apathy continued to progress with disease progression into Stages II–IV. Comparisons with other research in prodromal Huntington disease, however, are more central to the current findings. Kirkwood and colleagues (31) followed 45 prodromal gene mutation carriers and reported a greater increase in psychiatric abnormalities over an interval of 3.7 years. The greatest changes were noted in Irritability and Hostility. More recently, Tabrizi and colleagues (32) followed 120 prodromal Huntington disease gene mutation carriers and reported worsening apathy over 36 months. The current findings replicate and extend these reports and provide confidence that

the psychiatric symptoms seen in Huntington disease progress with disease severity and are likely secondary to the neurodegenerative disease process.

The detection of neurodegenerative diseases has progressed considerably as reflected in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. In this latest edition the field describes the emergence of mild cognitive impairment (MCI) as a precursor, or prodromal stage, evident in progressive brain disease. MCI in Huntington disease has been documented in at least 40% of persons carrying the gene mutation (33, 34), and numerous publications demonstrate that cognitive decline can be detected a decade prior to motor onset (35). Given the plethora of publications demonstrating early cognitive decline in Huntington disease in concert with the findings of our study showing psychiatric symptom progression prior to motor onset, the mono-symptomatic diagnostic criteria seems out of date. Since mental health professionals may see prodromal Huntington disease in clinical practice a decade before movement disorder specialists, an earlier diagnosis may be prudent for many individuals.

The current findings suggest the source of measurement can significantly alter psychiatric outcomes in prodromal and diagnosed Huntington disease. All findings from this research were more robust when psychiatric symptoms were rated by companions (rather than self-reported by gene-expanded participants) for prodromal Huntington disease. For instance, companion ratings worsened over time for 11/12 symptoms in the prodromal Huntington disease group with a high probability of imminent motor diagnosis, 6/12 symptoms in those with a medium probability of diagnosis and 2/12 symptoms in persons considered to be far from their estimated motor onset. Only 7/12 participant ratings showed significant change over time and only in the group in closest proximity to motor diagnosis. When analyses were conducted to examine the importance of discrepant ratings between the companion and the prodromal Huntington disease participants, findings showed that ratings on 7/12 psychiatric symptom scales were inconsistent between the raters. In participants closer to estimated motor onset, the companion ratings appear to be more valid and self-reported psychiatric symptoms may be more appropriate in gene-mutation carriers who are furthest from estimated motor onset.

These findings are consistent with prior cross-sectional observations that individuals with Huntington disease have decreased awareness of symptoms (36–39). Previous studies on awareness described above were cross-sectional (although Ho et al. had two time points, they were only about six weeks apart) and involved individuals diagnosed with Huntington disease. It is important to note that, even in Huntington disease mutation carriers who do not yet have motor diagnosis, decreased awareness of both motor (22) and psychiatric (4) symptoms have been documented. The current findings are the first to provide longitudinal data of reduced awareness in a prodromal Huntington disease cohort over such a long follow-up time period. Our findings indicate unawareness increases in concert with Huntington disease progression during the prodromal Huntington disease stages as indicated by participant-companion differences arising mostly in the Medium and High CAG-Age Product groups.

Difficulties with awareness or insight occur across the spectrum of neuropsychiatric disorders, including stroke, brain injury, dementia, psychosis, and mood disorders (40). The etiologies of these disparate conditions vary, and it is not known whether there are common mechanisms that underlie the development of unawareness between disorders. Several studies in different disorders have noted associations between deceased awareness of symptoms and pathology in the right hemisphere, dorsolateral frontal, and less often the parieto-temporal region. However, the findings are not consistent enough to indicate shared mechanisms with certainty. The results presented here and in other studies on Huntington disease symptoms and brain pathology are consistent with these anatomic findings, but more research is needed to support this connection. As described previously by others (41), it is likely that neural networks connecting several regions are responsible for the phenomenon of decreased awareness. The presentation of lack of awareness also varies among disorders. In fronto-temporal dementia, for example, insight is reduced early in the course of the illness, while this is a later manifestation in Alzheimer dementia (42). Unawareness is also irreversible in dementias, while it is often transient in other disorders such as stroke, traumatic brain injury, mood disorders, or schizophrenia. The progressive brain degeneration that occurs in Huntington disease may indicate reduced insight is permanent but additional study is needed to understand its course and causes in the illness. There are some limitations to consider in the interpretation of these results. Some issues relate to the nature of the assessments. It is important to note that individuals are asked to provide ratings over the previous seven days for the SCL-90-R. As these measures are obtained annually, they may miss episodes of psychopathology that occur between assessments. While these findings support changes in participant-companion reporting over time, more detailed assessments at more time points would be beneficial. Another issue relates to potential biases of the raters. Both participants and companions are aware of the Huntington disease genetic status of the participants, which may affect their perception of how they rate their symptoms. Selection bias of the sample may also impact the generalizability of these results. Only a fraction of those at risk for Huntington disease obtain genetic testing, which is required prior to enrollment in the PREDICT-HD study. There may be factors unique to those who obtain genetic testing and participate in research studies not present in the Huntington disease population. It is interesting to observe, however, that a recent study of premanifest Huntington disease not requiring known genetic status, and thus no predictive genetic testing, showed highly similar demographics, including education (43). Differences in awareness may also be present in our sample compared to the overall population. However, as previously described by Duff and colleagues (4), it is equally likely that individuals with lower or higher awareness would participate in the study. Despite these limitations, the results here provide initial information regarding psychiatric symptoms that occur in individuals who will develop Huntington disease and the importance of obtaining assessments from companions. This is critical to consider in future studies that assess behavioral manifestations and psychiatric symptoms, including those that investigate their underlying pathophysiology in Huntington disease and in therapeutic trials, as well as clinical assessment and management of persons who will develop Huntington disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Appendix

Location of Work

Department of Psychiatry, Carver College of Medicine, The University of Iowa, Iowa City, IA, USA

PREDICT-HD Investigators, Coordinators, Motor Raters, Cognitive Raters

Isabella De Soriano, Courtney Shadrick, and Amanda Miller (University of Iowa, Iowa City, Iowa, USA);

Edmond Chiu, Joy Preston, Anita Goh, Stephanie Antonopoulos, and Samantha Loi (St. Vincent's Hospital, The University of Melbourne, Kew, Victoria, Australia);

Phyllis Chua and Angela Komiti (The University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, Australia);

Lynn Raymond, Joji Decolongon, Mannie Fan, and Allison Coleman (University of British Columbia, Vancouver, British Columbia, Canada);

Christopher A. Ross, Mark Varvaris, Maryjane Ong, and Nadine Yoritomo (Johns Hopkins University, Baltimore, Maryland, USA);

William M. Mallonee and Greg Suter (Hereditary Neurological Disease Centre, Wichita, Kansas, USA);

Ali Samii, Emily P. Freney, and Alma Macaraeg (University of Washington and VA Puget Sound Health Care System, Seattle, Washington, USA);

Randi Jones, Cathy Wood-Siverio, and Stewart A. Factor (Emory University School of Medicine, Atlanta, Georgia, USA);

Roger A. Barker, Sarah Mason, and Natalie Valle Guzman (John van Geest Centre for Brain Repair, Cambridge, UK);

Elizabeth McCusker, Jane Griffith, Clement Loy, Jillian McMillan, and David Gunn (Westmead Hospital, Sydney, New South Wales, Australia);

Michael Orth, Sigurd Süβmuth, Katrin Barth, Sonja Trautmann, Daniela Schwenk, and Carolin Eschenbach (University of Ulm, Ulm, Germany);

Kimberly Quaid, Melissa Wesson, and Joanne Wojcieszek (Indiana University School of Medicine, Indianapolis, Indiana, USA);

Mark Guttman, Alanna Sheinberg, Albie Law, and Irita Karmalkar (Centre for Addiction and Mental Health, University of Toronto, Markham, Ontario, Canada);

Susan Perlman and Brian Clemente (UCLA Medical Center, Los Angeles, California, USA);

Michael D. Geschwind, Sharon Sha, Joseph Winer, and Gabriela Satris (University of California, San Francisco, San Francisco, California, USA);

Tom Warner and Maggie Burrows (National Hospital for Neurology and Neurosurgery, London, UK);

Anne Rosser, Kathy Price, and Sarah Hunt (Cardiff University, Cardiff, Wales, UK);

Frederick Marshall, Amy Chesire, Mary Wodarski, and Charlyne Hickey (University of Rochester, Rochester, New York, USA);

Peter Panegyres, Joseph Lee, Maria Tedesco, and Brenton Maxwell (Neurosciences Unit, Graylands, Selby-Lemnos & Special Care Health Services, Perth, Western Australia, Australia);

Joel Perlmutter, Stacey Barton, and Shineeka Smith (Washington University, St. Louis, Missouri, USA);

Zosia Miedzybrodzka, Daniela Rae, Vivien Vaughan, and Mariella D'Alessandro (Clinical Genetics Centre, Aberdeen, Scotland, UK);

David Craufurd, Judith Bek, and Elizabeth Howard (University of Manchester, Manchester, UK);

Pietro Mazzoni, Karen Marder, and Paula Wasserman (Columbia University Medical Center, New York, New York, USA);

Rajeev Kumar, Diane Erickson, Christina Reeves, and Breanna Nickels (Colorado Neurological Institute, Englewood, Colorado, USA);

Vicki Wheelock, Lisa Kjer, Amanda Martin, and Sarah Farias (University of California, Davis, Sacramento, California, USA);

Wayne Martin, Oksana Suchowersky, Pamela King, Marguerite Wieler, and Satwinder Sran (University of Alberta, Edmonton, Alberta, Canada);

Anwar Ahmed, Stephen Rao, Christine Reece, Alex Bura, and Lyla Mourany (Cleveland Clinic Foundation, Cleveland, Ohio, USA);

Executive Committee

Principal Investigator Jane S. Paulsen, Jeffrey D. Long, Hans J. Johnson, Thomas Brashers-Krug, Phil Danzer, Amanda Miller, H. Jeremy Bockholt, and Kelsey Montross.

Scientific Consultants

Deborah Harrington (University of California, San Diego); Holly Westervelt (Rhode Island Hospital/Alpert Medical School of Brown University); Elizabeth Aylward (Seattle Children's Research Institute); Stephen Rao (Cleveland Clinic); David J. Moser, Janet Williams, Nancy Downing, Vincent A. Magnotta, Hans J. Johnson, Thomas Brashers-Krug, Jatin Vaidya, Daniel O'Leary, and Eun Young Kim (University of Iowa).

Core Sections

Biostatistics

Jeffrey D. Long, Ji-In Kim, Spencer Lourens (University of Iowa); Ying Zhang and Wenjing Lu (University of Indiana).

Ethics

Cheryl Erwin (Texas Tech University Health Sciences Center); Thomas Brashers-Krug, Janet Williams (University of Iowa); and Martha Nance (University of Minnesota).

Biomedical Informatics.

H. Jeremy Bockholt, Jason Evans, and Roland Zschiegner (University of Iowa).

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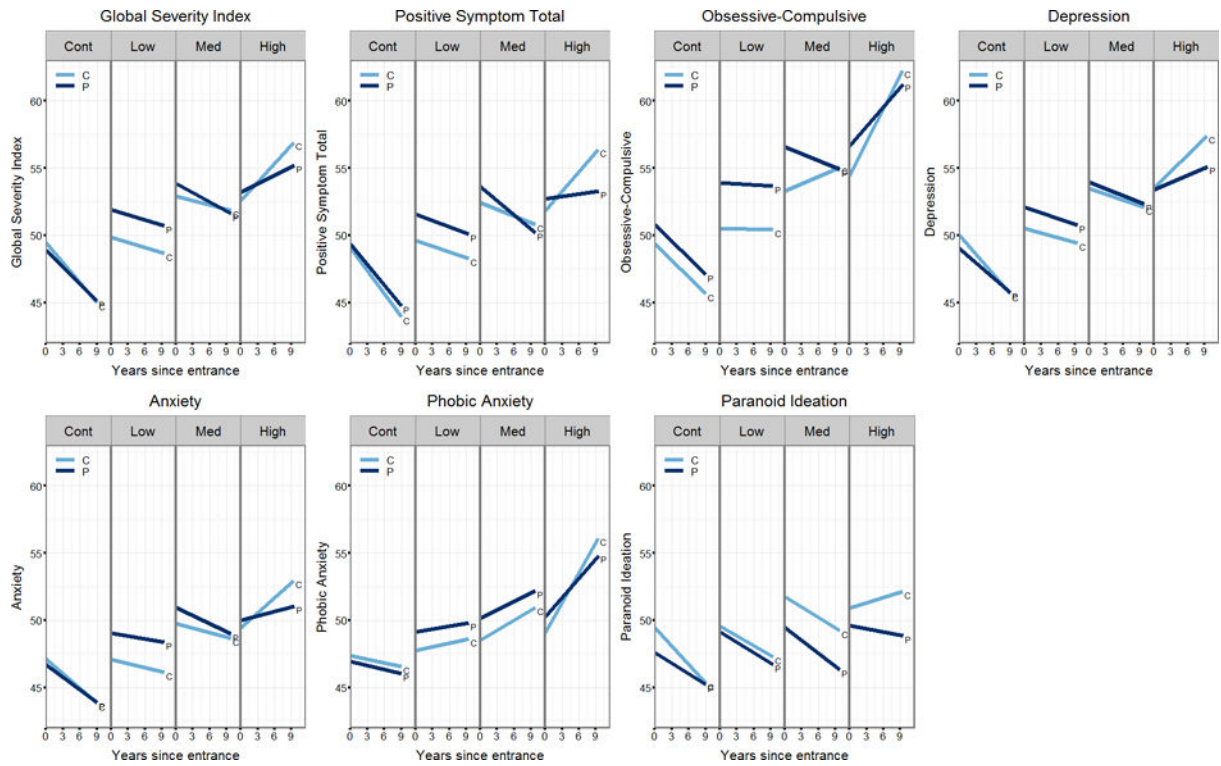
Figure 1.
Fitted Linear Mixed-Effects Regression (LMER) curves by group for participant and companion Symptom Checklist-90-Revised (SCL-90-R) ratings. All model coefficients were estimated adjusting for gender, years of education, and age at entry. The plots show the SCL-90-R score as a function of duration, person (participant or companion) and group. Low, Med, High indicate low, medium, or high probability of diagnosis within five years as estimated by CAG-Age Product (CAP) score.

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TABLE 1

Participant characteristics at study entry

		Group				Group Comparison
		Control	Low	Medium	High	
N of participants		298	280	356	371	
N of companions		282	262	335	356	
Sex (% female)		64.43	67.5	65.45	58.76	$X^2(3)=6.21$ (p=0.10)
Age (years)	Mean	44.11	34.16	40.45	44.42	$F(3,1301)=66.45$ (p<0.001)
	SD	11.76	8.47	9.6	10.34	
CAG repeat	Median	19	41	42	43	$F(3,1291)=4985.84$ (p<0.001)
	Range	12–35	36–47	38–49	39–61	
Education (years)	Mean	14.85	14.51	14.54	14.18	$F(3,1301)=3.58$ (p=0.014)
	SD	2.57	2.47	2.62	2.79	

Low, Med, High indicate low, medium, or high probability of diagnosis within five years as estimated by CAG-Age Product (CAP) score.

TABLE 2

Model comparison for participant and companion SCL-90-R measures

Variable	Model	Group Effect	Participant AICc	Participant dAICc	Participant wAICc	Companion AIC	Companion dAICc	Companion wAICc
GSI	1	Null	44820.28	31.77	0.00	40001.38	54.79	0.00
	2	Baseline	44792.62	4.11	0.11	39968.83	22.24	0.00
	3	**Baseline + Longitudinal**	**44788.51**	**0.00**	**0.89**	**39946.59**	**0.00**	**1.00**
PST	1	Null	42831.61	33.29	0.00	38466.49	68.84	0.00
	2	Baseline	42805.20	6.88	0.03	38430.43	32.78	0.00
	3	**Baseline + Longitudinal**	**42798.31**	**0.00**	**0.97**	**38397.65**	**0.00**	**1.00**
PSDI	1	Null	45463.96	23.74	0.00	40298.05	41.08	0.00
	2	Baseline	45445.56	5.35	0.07	40263.78	6.82	0.03
	3	**Baseline + Longitudinal**	**45440.22**	**0.00**	**0.94**	**40256.97**	**0.00**	**1.00**
SOM	**1**	**Null**	**42803.06**	**0.00**	**0.46**	37634.13	10.62	0.01
	2	Baseline	42803.70	0.64	0.34	37633.26	9.75	0.01
	3	Baseline + Longitudinal	42804.76	1.70	0.20	**37623.51**	**0.00**	**0.99**
O-C	1	Null	46037.23	66.08	0.00	40225.99	90.69	0.00
	2	Baseline	45983.99	12.84	0.00	40165.93	30.63	0.00
	3	**Baseline + Longitudinal**	**45971.15**	**0.00**	**1.00**	**40135.30**	**0.00**	**1.00**
I-S	1	Null	45460.40	21.75	0.00	40387.99	32.74	0.00
	2	Baseline	45439.80	1.16	0.36	40364.90	9.65	0.01
	3	**Baseline + Longitudinal**	**45438.64**	**0.00**	**0.64**	**40355.25**	**0.00**	**0.99**
DEP	1	Null	46069.77	30.01	0.00	40702.42	55.57	0.00
	2	Baseline	46040.05	0.29	0.46	40663.07	16.22	0.00
	3	**Baseline + Longitudinal**	**46039.76**	**0.00**	**0.54**	**40646.85**	**0.00**	**1.00**
ANX	1	Null	44524.35	24.61	0.00	39287.96	43.24	0.00
	2	**Baseline**	**44499.73**	**0.00**	**0.51**	39260.88	16.16	0.00
	3	Baseline + Longitudinal	44499.82	0.09	0.49	**39244.72**	**0.00**	**1.00**

Variable	Model	Group Effect	Participant AICc	Participant dAICc	Participant wAICc	Companion AIC	Companion dAICc	Companion wAICc
HOS	1	Null	45763.65	33.04	0.00	41923.67	36.12	0.00
	2	Baseline	45731.09	0.48	0.44	41889.31	1.77	0.29
	3	**Baseline + Longitudinal**	**45730.61**	**0.00**	**0.56**	**41887.55**	**0.00**	**0.71**
PHOB	1	Null	44385.08	21.60	0.00	38414.95	25.84	0.00
	2	Baseline	44368.30	4.82	0.08	38405.41	16.30	0.00
	3	**Baseline + Longitudinal**	**44363.48**	**0.00**	**0.92**	**38389.11**	**0.00**	**1.00**
PAR	1	Null	41461.59	6.78	0.02	39364.64	13.05	0.00
	2	**Baseline**	**41454.81**	**0.00**	**0.64**	**39351.59**	**0.00**	**1.00**
	3	Baseline + Longitudinal	41456.09	1.28	0.34	39391.12	39.53	0.00
PSY	1	Null	45879.04	29.96	0.00	40685.39	35.15	0.00
	2	**Baseline**	**45849.08**	**0.00**	**0.66**	**40653.05**	**2.81**	**0.20**
	3	Baseline + Longitudinal	45850.41	1.33	0.34	40650.24	**0.00**	**0.80**

The models with smallest AICc values are the best models and are displayed in boldface type. Models with smaller dAICc and wAICc closest to 1 indicate better fit. GSI=Global Severity Index; PST=Positive Symptom Total; PSDI=Positive Symptom Distress Index; SOM=Somatization; O-C=Obsessive–Compulsive; I-S=Interpersonal Sensitivity; DEP=Depression; ANX=Anxiety; HOS=Hostility; PHOB=Phobic Anxiety; PAR=Paranoid Ideation; PSY=Psychoticism.

TABLE 3

Baseline and Longitudinal prodromal HD group differences relative to controls for participant (P) and companion (C) SCL-90-R

| Measure | Baseline Group Difference Relative to Controls | | | | | | | | | | | |
| | Low | | | | Medium | | | | High | | | |
	Est	SE	tval	pval	Est	SE	tval	pval	Est	SE	tval	pval
P GSI	2.54	1.14	2.23	0.026 *	4.89	1.03	4.74	<0.001 ***	4.32	1.02	4.24	<0.001 ***
P PST	2.03	0.97	2.10	0.036 *	4.24	0.88	4.84	<0.001 ***	3.31	0.86	3.83	<0.001 ***
P PSDI	3.15	0.92	3.43	<0.001 ***	3.55	0.83	4.26	<0.001 ***	2.76	0.82	3.36	<0.001 ***
P O-C	2.81	1.19	2.36	0.018 *	5.81	1.08	5.38	<0.001 ***	6.02	1.07	5.65	<0.001 ***
P I-S	2.24	1.12	2.01	0.045 *	3.46	1.01	3.42	<0.001 ***	3.94	1.00	3.95	<0.001 ***
P DEP	2.78	1.12	2.49	0.013 *	4.89	1.01	4.84	<0.001 ***	4.39	1.00	4.40	<0.001 ***
P ANX	2.08	0.94	2.20	0.028 *	4.14	0.85	4.87	<0.001 ***	3.94	0.84	4.71	<0.001 ***
P HOS	2.98	1.06	2.81	0.005 **	5.21	0.96	5.42	<0.001 ***	4.44	0.95	4.67	<0.001 ***
P PHOB	1.46	0.96	1.52	0.13	2.92	0.87	3.36	<0.001 ***	3.12	0.86	3.64	<0.001 ***
P PAR	1.42	0.75	1.89	0.059	1.70	0.68	2.50	0.013 *	2.35	0.67	3.52	<0.001 ***
P PSY	2.86	1.09	2.61	0.009 **	4.52	0.99	4.59	<0.001 ***	5.55	0.97	5.72	<0.001 ***
C GSI	0.87	1.07	0.81	0.417	3.59	0.97	3.71	<0.001 ***	3.21	0.95	3.38	<0.001 ***
C PST	0.94	0.98	0.96	0.338	3.46	0.89	3.91	<0.001 ***	2.96	0.87	3.39	<0.001 ***
C PSDI	0.64	0.95	0.67	0.504	3.09	0.87	3.56	<0.001 ***	2.80	0.85	3.29	0.001 **
C SOM	−0.35	0.84	−0.42	0.674	1.14	0.76	1.50	0.134	−0.18	0.74	−0.25	0.804
C O-C	1.56	1.08	1.45	0.148	4.09	0.98	4.18	<0.001 ***	5.18	0.96	5.40	<0.001 ***
C I-S	1.00	1.10	0.91	0.363	2.86	1.00	2.86	0.004 **	2.94	0.98	3.00	0.003 **
C DEP	0.80	1.08	0.74	0.460	3.51	0.98	3.56	<0.001 ***	3.53	0.97	3.65	<0.001 ***
C ANX	0.42	0.91	0.47	0.639	2.76	0.82	3.36	<0.001 ***	2.34	0.81	2.90	0.004 **
C HOS	2.36	1.25	1.88	0.059	4.56	1.14	4.00	<0.001 ***	4.41	1.12	3.94	<0.001 ***
C PHOB	0.69	0.77	0.90	0.370	1.36	0.69	1.97	0.049 *	1.75	0.68	2.57	0.010 *

Baseline Group Difference Relative to Controls

Measure	Low				Medium				High			
	Est	SE	tval	pval	Est	SE	tval	pval	Est	SE	tval	pval
C PAR	0.76	0.86	0.88	0.378	2.81	0.78	3.61	<0.001***	2.66	0.76	3.49	<0.001***
C PSY	2.60	1.02	2.55	0.011*	4.03	0.93	4.35	<0.001***	3.37	0.91	3.70	<0.001***

Longitudinal Group Difference Relative to Controls

Measure	Low				Medium				High			
	Est	SE	tval	pval	Est	SE	tval	pval	Est	SE	tval	pval
P GSI	0.21	0.21	1.02	0.308	0.05	0.19	0.26	0.796	0.51	0.19	2.74	0.006**
P PST	0.27	0.17	1.54	0.124	0.06	0.16	0.35	0.73	0.49	0.16	3.10	0.002**
P PSDI	−0.18	0.20	−0.93	0.354	−0.05	0.19	−0.29	0.772	0.37	0.18	2.04	0.041*
P O-C	0.32	0.23	1.41	0.157	0.16	0.21	0.76	0.448	0.81	0.21	3.93	<0.001***
P I-S	0.26	0.21	1.22	0.222	0.20	0.20	1.02	0.306	0.51	0.19	2.61	0.009**
P DEP	0.11	0.21	0.51	0.613	0.07	0.20	0.37	0.714	0.42	0.19	2.19	0.028*
P HOS	−0.05	0.21	−0.24	0.809	−0.27	0.20	−1.36	0.175	0.19	0.20	0.95	0.340
P PHOB	0.13	0.19	0.67	0.506	0.26	0.18	1.43	0.153	0.55	0.18	3.08	0.002**
C GSI	0.40	0.22	1.82	0.069	0.51	0.20	2.50	0.012*	1.04	0.20	5.21	<0.001***
C PST	0.45	0.19	2.35	0.019*	0.48	0.18	2.69	0.007**	1.08	0.18	6.14	<0.001***
C PSDI	0.31	0.22	1.44	0.150	0.27	0.20	1.31	0.191	0.69	0.20	3.46	<0.001***
C SOM	0.39	0.16	2.38	0.017*	0.38	0.15	2.46	0.014*	0.60	0.15	3.98	<0.001***
C O-C	0.44	0.24	1.84	0.065	0.65	0.22	2.90	0.004**	1.30	0.22	5.90	<0.001***
C I-S	0.09	0.22	0.42	0.672	0.23	0.20	1.16	0.246	0.70	0.20	3.50	<0.001***
C DEP	0.43	0.23	1.87	0.062	0.46	0.22	2.14	0.032*	0.99	0.21	4.67	<0.001***
C ANX	0.27	0.19	1.42	0.155	0.36	0.18	1.99	0.047*	0.81	0.18	4.54	<0.001***
C HOS	0.08	0.26	0.32	0.749	0.29	0.24	1.20	0.230	0.59	0.24	2.49	0.013*
C PHOB	0.16	0.20	0.79	0.430	0.29	0.19	1.56	0.118	0.79	0.18	4.31	<0.001***
C PSY	−0.12	0.23	−0.50	0.619	0.17	0.22	0.78	0.435	0.47	0.22	2.18	0.029*

P=participant; C=companion; GSI=Global Severity Index; PST=Positive Symptom Total; PSDI=Positive Symptom Distress Index; O-C=Obsessive–Compulsive; I-S=Interpersonal Sensitivity; DEP=Depression; ANX=Anxiety; HOS=Hostility; PHOB=Phobic Anxiety; PAR=Paranoid Ideation; PSY=Psychoticism; SOM=Somatization. Low, Med, High indicate low, medium, or high probability of diagnosis within five years as estimated by CAG-Age Product (CAP) score.

***
$p < 0.001$,

**
$p < 0.01$,

*
$p < 0.05$,

TABLE 4

Slope discrepancy between participants and companions by group as measured by the sum of weights over all models with unequal group slopes

Measure	Control	Low	Medium	High
GSI	0.43	0.27	0.55	**0.80**
PST	0.39	0.28	**0.73**	**0.99**
PSDI	0.45	0.54	0.28	0.28
SOM	0.67	0.33	0.51	0.40
O-C	0.27	0.28	**0.89**	**0.90**
I-S	0.27	0.33	0.28	0.44
DEP	0.50	0.28	0.30	**0.75**
ANX	0.34	0.31	0.49	**0.86**
HOS	0.41	0.28	0.58	0.36
PHOB	0.27	0.29	0.33	**0.81**
PAR	0.66	0.28	0.42	**0.80**
PSY	0.29	0.43	0.34	0.29

Values close to 1 indicate higher importance. Weights > 0.7 are displayed in boldface type. Low, Med, High indicate low, medium, or high probability of diagnosis within five years as estimated by CAG-Age Product (CAP) score. GSI=Global Severity Index; PST=Positive Symptom Total; PSDI=Positive Symptom Distress Index; SOM=Somatization; O-C=Obsessive–Compulsive; I-S=Interpersonal Sensitivity; DEP=Depression; ANX=Anxiety; HOS=Hostility; PHOB=Phobic Anxiety; PAR=Paranoid Ideation; PSY=Psychoticism.