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Implications of Differential Associations of Neuroticism Facets With Cognitive Function in Late Life Depression

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Dr. Manning's study sheds light on several important, and as yet poorly understood, aspects of the role of personality in cognitive decline within late life depression (LLD). The paper draws attention to the fact that Neuroticism, one of the “Big 5” dimensions of personality, is actually a compound trait composed of several distinct facets. Only some of these specific traits are related to depression treatment response and cognitive trajectory. Some key implications are outlined in Table 1 and disussed further below.

While it has been known for some time that Neuroticism in general is predictive of worse psychiatric outcomes, it is helpful from a prognostic standpoint to clarify the particular elements of Neuroticism involved. One surprising finding is that propensity toward dysphoric and anxious affect, the “depression” and anxiety facets of Neuroticism respectively, are only modestly (by size of regression coefficient) and non-significantly (with respect to formal null hypothesis tests) associated with depression treatment response. Instead, the more important traits are vulnerability to stress (VS)—tapped by items such as “I often feel as if I am going to pieces”[1], Impulsiveness (e.g., “I have trouble resisting my craving”), and perhaps angry hostility (e.g., “I often get angry at the way people treat me”). Isolating these specific tendencies provides clues about why Neuroticism, as a general tendency, seems to complicate LLD treatment.

It is also now relatively well established that Neuroticism is a risk factor for dementia[2]. Again however, most studies have difficulty untangling exactly what it is about general Neuroticism that drives this risk. The term “proneness to distress” [3] has been used to describe Neuroticism in its relation to dementia risk, and is consistent with Dr. Manning's finding regarding the VS facet of broader Neuroticism. The “distress proneness” terminology used sometimes to refer to the entire Neuroticism dimension reflects the prevailing model in which stress reactivity leads to over-activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, resulting in chronic glucocorticoid dysfunction leading to hippocampal over time. Indeed, data suggest links between Neuroticism and global as well as prefrontal and medial temporal cortical atrophy [4], but curiously Neuroticism seems unassociated with amyloid-beta, tau protein, or Lewy-bodies pathology [3]. A more recent effort identified associations between global Neuroticism and tau but not amyloid pathology, but these were driven by the angry hostility and anxiety facets[5]. VS, instead, was related to cognitive function. Dr. Manning's report reinforces the importance of VS as a prognostic factor of cognitive performance, but underscores the importance of understanding the complex mechanisms at the nexus of personality phenotype, manifest cognition, and neuropathology.

Typically, the first consideration upon having identified a robust risk factor is how it can be modified. That matter becomes complex when dealing with aspects of personality, particularly in later life. The topic of whether and how health-damaging personality tendencies might be modified has been considered in detail recently by a National Institute on Aging work group[6]. One alternative to attempting direct modification of a personality trait, particularly in later life when it may have already exerted its impact for decades, is to capitalize on its potency as a prognostic or predictive factor[6]. Risk prediction models can inform clinical care in many ways, including designing an appropriate schedule of follow-ups or surveillance visits; weighing costs-vs.-benefits of prevention and early intervention efforts, in light of estimated risk; planning the timing and perhaps form of intervention, if etiologic information is conveyed by the risk model; and informing patients, families, and other members of the care team so that they can act as they see fit.

Polygenic risk scores have dominated prediction model efforts lately, but often neglect relevant clinical, environmental, or social-behavioral data that could improve their performance and capture other vital aspects of patient risk. In part to overcome this, the recent Precision Medicine initiative explicitly emphasized the inclusion of environmental factors and behavioral phenotype in conjunction with genetic predictors of disease. Personality traits may represent one non-genomic area for consideration in predictive models, as they reflect the result of a swath of genetic and environmental factors and index a wide range of risk behavior. Personality traits are also assessed inexpensively and non-invasively. Finally, the may indicate susceptibility to cognitive dysfunction long before noticeable clinical signs. Given the absence of disease-altering therapies in this area, targeted prevention—and hence, accurate risk stratification—is needed very early in the process. Results like those of Dr. Manning's study provide clues about specific elements of personality that might be incorporated into comprehensive prediction models.

Dr. Manning fully acknowledges the limitations of a mixed retrospective-prospective design. It should be noted that the statistics reported are perfectly valid as estimates of the association between a factor measured at one point (Neuroticism traits) and the rate of linear decline over time in another factor (depressive symptoms, cognitive function). It is just that the single snapshot measurement of personality occurs after some cognitive (or depressive symptom) change has occurred in an indeterminate number of patients. To the degree that worsening cognitive status increased Neuroticism between baseline and the measurement of Neuroticism, a degree of reverse causation could be mixed in. On the other hand, patients were being treated for depression, a countervailing influence that might reduce Neuroticism scores[7]. Personality changes in early stages of cognitive decline would also be expected to be slight, and the sample averages in the normal CERAD range at baseline. Therefore I suspect the estimates reflect a substantial prospective component, despite the ambiguity of personality measurement timing. In future analyses of such designs, it would appear possible to control for time from entry to personality assessment, and perhaps to examine a time-since-entry*Neuroticism interaction term. Such challenges illustrate the reality of pragmatic clinical research. The power and breadth of a huge epidemiologic cohort is traded for in-depth measurement (the full 240-item NEO-PI R, a substantial cognitive battery) and a clinically relevant sample. Although the design is not perfectly pure (few are), it still

provides valuable information about the phenomenon in question that we did not have before, and gives us important clues for follow-up work.

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Table 1

Key Points

1	Neuroticism is a multifaceted propensity toward negative affect. Dr. Manning's paper pinpoints one specific element of Neuroticism, *vulnerability to stress*, as a particularly potent risk factor for poor depression treatment response and for cognitive decline. Vulnerability to stress is operationalized by a common personality scale with items like “I often feel helpless and want someone else to solve my problems” and “When I'm under a great deal of stress, sometimes I feel like I'm going to pieces.”
2	Neuropathological mechanisms have been proposed to account for links between distress proneness and cognitive decline. However, mechanisms are likely complex and have yet to be definitively characterized.
3	Opinions vary about the feasibility of directly modifying personality traits in late life. An alternative approach would be to examine whether measures of personality phenotype can be leveraged in clinical prediction models of the course of disease, similar to the prediction models based on prognostic genotypes. Accurate and reliable predictions could inform treatment planning and decision-making.