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Indicators of Early Adult and Current Personality in Parkinson's Disease

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by

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Dedication

This work is dedicated to my family, who supported and encouraged me throughout this process; to my mother who read to me as a child, encouraged my curiosity, and taught me by her example that education is valuable beyond measure and is worth sacrifices; to my husband who sacrificed with me and has stayed beside me through every step of this process; and to my other family members whose support and encouragement has meant more than words can express. I love and appreciate you all.

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Abstract

Introduction: Previous epidemiologic studies suggest that the personality of Parkinson's disease (PD) patients differs from that of controls, and laboratory evidence supports a potential common pathophysiology of personality traits and PD. One nested case-control study found that PD cases were significantly more anxious than controls before the clinical onset of the disease, and additional data suggest that certain occupations may be risk factors for the disease. Additionally, the latent period that precedes the onset of motor symptoms of PD is unknown.

Objectives: The objectives of this study were to evaluate the association of PD with objective indicators of current and premorbid personality, to determine the correlation of early-adult life personality indicators with current personality characteristics and to evaluate the role of personality as indicated by occupational choice and employment patterns in the risk for PD using the Dictionary of Occupational Titles job classification system.

Methods: Eighty-nine cases and 99 controls completed in-person structured interviews. Assessments included measures of current personality characteristics and indicators of early-adult (ages 20-35 years) personality, such as activities and lifestyle patterns. Associations between these latent personality variables and current personality characteristics were studied using correlation, partialling out the effects of age, sex and

education. Multiple logistic regression was used to evaluate the associations of early-adult personality and occupational characteristics and the risk for Parkinson's disease.

Results: Cases with Parkinson's disease reported higher levels of neuroticism (OR=1.05 (95% CI 1.00-1.11)) and harm-avoidance (OR = 1.07 (95% CI 1.00-1.15)) compared with controls on measures of current personality. A stable association among many traits, particularly traits such as novelty-seeking, which are driven by dopaminergic function, was present not only among controls with presumably normal dopaminergic function throughout their lives, but also among cases. Early-adult life routinization was correlated with current levels of neuroticism (cases: r=0.33, p=0.01; controls: r=0.26, p=0.04), extraversion (cases: r=-0.33, p=0.01; controls: r=-0.33, p=0.04), novelty-seeking (cases: r=-0.33, p=0.015; controls: r=-0.34, p=0.007) and harm-avoidance (cases: r=0.47, p=0.0003; controls: r=0.45, p=0.0002) and for the association of early-adult life activity risks with harm-avoidance (cases: r=-0.47, p=0.0004; controls: r=-0.42, p=0.0006). Taking or wanting to take "activity risks," such as riding on roller coasters as a young adult was found to reduce the odds of Parkinson's disease (OR = 0.78 (95% CI 0.63-0.97)) in the entire sample, while higher levels of early-adult routinization were associated with a greater risk for Parkinson's disease among women (OR=1.63 (95% CI 1.05-2.53)). Parkinson's disease was inversely associated with the total number of jobs held (OR=0.87 (95% CI 0.75-0.99)) but not with the number of job categories or duration of the primary occupation. Increased complexity of work with people was associated with PD among women (OR=0.69 (95% CI 0.53-0.89), as was less complex work with things (OR=1.45 (95% CI 1.11-1.88). The complexity of work with data, people or things was

not associated with the risk for PD among men or in the sample as a whole. Men with PD whose work involved greater complexity with data took fewer activity risks (r=0.32, p=0.02) and reported greater routinization (r=-0.34, p=0.01) as a young adult.

Conclusions: This evaluation of early-adult risk factors advances current knowledge about the premorbid period of PD and supports the hypothesis that a long period of subclinical disease precedes the onset of motor symptoms. These findings validate the association of these early-adult personality traits and PD and support the idea that behaviors associated with PD personality exist many years before the presentation of motor symptoms. Dopaminergic aspects of personality were related to occupational choices and future consideration of this hypothesis is warranted. Since PD is a degenerative disorder, determining the age of onset of this illness is important in the search for modifiable risk factors and neuroprotective strategies.

Chapter 1

Introduction

Background and Significance

Parkinson's disease (PD)

The movement disorder of Parkinson's disease (PD) is a neurologic disorder caused by degeneration of dopaminergic neurons in the substantial nigra pars compacta [1]. It is characterized by resting tremor, bradykinesia (slowness in executing movements), rigidity and postural instability. Signs of PD start in one limb, usually an arm, and spread to the other limbs and eventually to the other side of the body as the disease progresses [2].

PD affects approximately 500,000 people in the US, including 1-3% of individuals aged >65 years and up to 10% of those >80 years [3, 4]. The annual incidence rate is approximately 16-18 per 100,000 and the mean age at onset is 60 years, but is difficult to pinpoint the exact age of onset because the disease onset is insidious [5]. Symptoms of PD are usually present 3-5 years before patients are diagnosed. Risk factors for PD include age [6-8], male sex (relative risk for men = 1.2-1.5) [6, 9], rural living and associated exposures including well water, pesticides, and herbicides [10-15], and

occupation as a farmer, physician, dentist, teacher, lawyer, or scientist [16-19]. Epidemiologic studies have demonstrated an inverse association between PD and smoking, coffee drinking, and alcohol intake [20, 21]. Many individual studies and a recent meta-analysis [22] reported a dose-response relation between cigarette smoking and risk for PD, and it has been theorized that nicotine may be neuroprotective against the disease [23]. The cause of PD is unknown. Other than these risk factors, ten genes have been identified as associated with PD including parkin, DJ1, PINK1, PARK2, PARK7, LRRK2, SNCA, GBA, SNCAIP, and UCHL1 [24, 25]. Many researchers believe that several factors combined are involved, including free radicals, accelerated aging, environmental toxins, and genetic predisposition.

Personality and PD

As early as 1913, the scientific literature discussed a distinct personality type observed in patients with PD [26]. Personality is an organized set of characteristics possessed by a person that uniquely influences motivations and behaviors in various situations [27]. Personality traits are highly stable during adulthood [28-30], although there is evidence for a “maturation effect” [31]. Levels of agreeableness and conscientiousness typically increase with time while extraversion, neuroticism, and openness tend to decrease. Personality is a latent construct that is not directly measurable and is thus difficult to quantify. Many theoretical approaches to conceptualizing and measuring personality have been proposed including the Five-factor model and the Temperament and Character Inventory, which are both used in this study.

PD patients have been described as rigid, cautious and introverted, and it has been suggested that PD could be associated with a specific personality type [32]. It is biologically plausible that patients with PD may have differences in their personality due to the role of dopamine and the neurophysiology of the reward system of the brain. The dopaminergic nuclei of the brain stem are not only involved in the pathophysiology of motor symptoms [33], but influence personality as well [34]. An association between dopamine D2 receptor binding and harm-avoidance has been demonstrated in normal individuals using positron emission tomography [35]. This relation of dopamine with personality characteristics has led to the hypothesis that when people approach novel stimuli, the normal pleasurable increase in dopamine is lessened in patients with PD resulting in fewer novelty-seeking behaviors (the "parkinsonian personality") [36]. Furthermore, studies have demonstrated that low dopamine is associated with lower novelty reactions in rats [37], and PET studies report an association between dopamine levels and novelty-seeking and harm avoidance behavior in healthy subjects [35, 38].

Cloninger proposed that temperament traits are primarily modulated by dopamine [34], and the D4 dopamine receptor exon III gene has been associated with a "novelty-seeking" personality [39]. Several case-control studies found that PD patients have reduced leadership tendencies, flexibility and sociability and are more quiet, generous, cautious, and even-tempered during the time period prior to the onset of PD compared with controls [40-42]. Retrospective assessment of personality also has shown that PD patients have high premorbid levels of introversion and obsessive-compulsive tendencies [43]. However, retrospective personality assessment is likely limited by the high potential

for recall bias associated with having a chronic disease as well as questionable accuracy in the determination of the time of disease onset. These results have not been confirmed in any other study using objective indicators of premorbid personality, such as risk-taking and preference for certain types of behavior.

Perhaps the best study of personality and PD was conducted within a historical cohort of 7,216 patients evaluated at the Mayo Clinic who were followed for approximately 40 years [44]. Sixty-eight incident PD cases were identified through a medical records database and from the Rochester Epidemiology Project. Baseline measures from the Minnesota Multiphasic Personality Inventory (MMPI) were compared with age- and sex-matched controls. High premorbid scores of anxiety were significantly associated with PD (OR=1.95; 95% CI = 1.08-3.54) and this association remained significant when subjects who developed PD within 5 and 10 years of baseline were excluded, lowering the possibility that the results could be explained by the disease. Other case-control studies have found reduced sensation-seeking [45], reduced novelty-seeking [36, 46] and higher harm-avoidance [46, 47] in cases with PD compared with normal [45, 46] and medical [36, 47] controls.

Previous studies of occupational risk factors for PD have yielded inconsistent results. A large study examined medical records of over 2,000 patients with PD and abstracted the primary occupation; a higher than expected history of employment in medicine (medicine and dentistry), farming, teaching, science, religion and legal fields was reported [48]. Conversely, a case-control study of 404 incident cases of PD did not find any association

between occupations related to farming, welding or pesticide exposure and PD [49] and a smaller study failed to find any association with occupations as well [50]. Other case-control studies have reported higher estimated risks of PD among physicians [51] and other health care workers [19], agriculture workers [52], hunters [52], forestry workers [52] teachers [19], and reduced risk among those employed in manufacturing [52], transportation [52] and the service industry [18]. Most occupational studies have focused on toxic exposures as potential mechanisms associated with risk for PD. However, occupational choice is affected by an individual's personality, and this aspect of occupation has only been examined in one recent study [53] which reported an association between PD and fewer occupational requirements of adaptability (OR=0.84 (95% CI 0.70-1.02)), ability to make generalizations (OR=0.85 (95% CI 0.72-1.00)), and preference for abstract activities (OR=0.90 (95% CI 0.76-1.06)). Given the role of dopamine and the neurophysiology of the reward system, it is plausible that individuals destined to develop PD have personality differences that may influence their occupational choices early in life.

Additional risk factors for PD include smoking, caffeine, and alcohol intake, which have been shown to be inversely associated with the risk for PD [20, 21]. Although it is possible that a biologic pathway explains the reduction in risk for PD among smokers, individuals who are destined to develop PD may have premorbid disorders of their reward system in early life that contribute to reduced voluntary exposure to these agents. Dopamine facilitates addiction and reinforces the addictive effects of behaviors such as smoking. An individual with low dopaminergic drive might derive a different

neurochemical reward from these behaviors compared with those with normal dopamine levels [54]. The dose-response relation observed in previous studies could reflect baseline differences in dopamine levels.

Rationale and Objectives

One knowledge gap in the field of PD is uncertainty about when the disease actually begins. PD is a neurodegenerative disorder and the motor signs of PD do not become apparent until 50-70% of substantia nigra neurons have degenerated [55]. Since PD is a degenerative disorder, determining the onset of this degeneration is important in the search for modifiable risk factors and neuroprotective strategies. Although it is logical that individuals with PD who have low levels of dopamine might have lower levels of these dopaminergic personality traits, it is of interest to know if personality differences were present prior to the onset of motor symptoms. Personality changes may manifest earlier in the disease process than motor symptoms and information about these differences and the timing of any differences would broaden the current understanding of the disease process.

Results from previous studies support the hypothesis that premorbid personality characteristics are associated with the risk for PD. However, these results have not been confirmed in any other study using objective indicators of premorbid personality, the time of onset of premorbid personality differences has not been objectively examined, nor have the number and variety of jobs been used as indicators of personality in studying the risk for PD.

The objectives of this study were to evaluate the role of current and premorbid personality in the risk for PD using objective personality indicators, determine the correlation of early-adult life personality indicators with current personality characteristics and thereby assess the probable time of onset of dopaminergic dysfunction in individuals with PD, and evaluate the role of personality as indicated by occupational choice and employment patterns in the risk for PD. Evaluation of early-adult risk factors will advance current knowledge about the premorbid period of the disease and will provide valuable information about the duration of the presymptomatic phase of the disease. Since PD is a degenerative disorder, determining the onset of this degeneration is important in the search for modifiable risk factors and neuroprotective strategies.

Specific Aims

While a large prospective study might best answer the question of temporal effects of personality on the risk for PD, such a study would require vast financial resources and an unrealistic period of follow-up. An alternative design is to use objective, retrospective measures as indicators of personality in a period of time that clearly precedes the onset of PD.

Our primary objective was to evaluate whether subjects who have PD have distinct behaviors related to personality characteristics that precede the motor symptoms of their disease by many years. This study aimed to test the hypothesis that personality characteristics in early adulthood, inferred from objective behaviors well before the onset of motor symptoms of PD, are associated with the risk for PD.

The papers presented in the following sections each address one of the following Specific Aims:

Aim I

Determine whether premorbid personality indicators correlate with current personality characteristics in both cases and controls (Paper 1).

To examine how objective indicators of premorbid personality are associated with current personality traits (NEO-FFI and TCI), Pearson rank correlation coefficients were calculated to determine whether early-adulthood personality indicators correlate with current personality characteristics. Separate analyses were conducted for cases and controls to examine whether cases' (but not controls') indicators changed (presumably as a result of their disease) after PD onset. Our hypothesis was that these may change in cases but would be more stable among controls. Latent factors, identified by factor analysis of the early-adulthood personality indicators, were examined to determine if they correlate with current personality factors.

Aim II

Evaluate whether premorbid personality is a risk factor for PD (Paper 2).
Personality indicators included indicators such as preferences, habits and elective activities in early adulthood. These measures served as indicators of personality traits including risk-taking, sensation-seeking, and routinized behavior of cases and controls.

Our hypothesis was that cases with PD would be less likely to have engaged or wanted to have engaged in risky activities and behaviors and would report a preference for routine in the years prior to the onset of their disease. Each measure was examined for its distribution in cases and controls. For each premorbid personality indicator, Odds Ratios and their 95% Confidence Intervals were derived from stratified and logistic regression analyses.

Aim III

Examine occupational histories as an indicator of personality and the association between occupational choices and the risk for PD (Paper 3).

Occupational histories can indicate personality characteristics such as risk-taking and novelty-seeking through frequent job changes and transitions between industries. Utilizing the Dictionary of Occupational Titles (DOT) job classification system, the complexity of subjects' main occupations with regard to people, data and things was evaluated as possible risk factors for PD. We hypothesized that cases would have fewer job changes and would work in occupations requiring greater complexity with data and less complexity with people or things compared to controls.

Chapter 2

Early-Adult Life Correlates of Personality in Parkinson's Disease

Abstract

Introduction: Parkinson's disease (PD) patients have been described as having an introverted, rigid and harm-avoidant personality, present decades before motor symptoms begin. Previous studies have relied on subjective reports about patients' previous personality.

Objective: The objectives of this study were to examine current personality profiles of PD patients and to assess how personality indicators of early-adult life correlate with current personality.

Methods: Data were collected from 89 PD cases and 99 controls through in-person assessments of current personality characteristics and early-adult life personality indicators based on activities and lifestyle patterns during ages 20-35 years. Associations of latent variables representing early-adult activity risks, lifestyle risks and routinization with current personality characteristics were studied using Pearson correlations, partialling out the effects of age, sex and education.

Results: Greater current levels of neuroticism (OR=1.05 (95% CI 1.00-1.11)) and harm-avoidance (OR=1.07 (95% CI 1.00-1.15)) were evident in cases compared to controls, adjusting for age, sex and education. Significant correlations between early-life indicators

and late-life personality characteristics were consistent among cases and controls for associations of early-adult life routinization with current measures of neuroticism (cases: r=0.33, p=0.01; controls: r=0.26, p=0.04), extraversion (cases: r=-0.33, p=0.01; controls: r=-0.33, p=0.04), novelty-seeking (cases: r=-0.33, p=0.015; controls: r=-0.34, p=0.007) and harm-avoidance (cases: r=0.47, p=0.0003; controls: r=0.45, p=0.0002) and for early-adult life activity risks with harm-avoidance (cases: r=-0.47, p=0.0004; controls: r=-0.42, p=0.0006).

Conclusion: Current personality profile of PD cases, reflected by higher neuroticism and harm-avoidance, may reflect stable personality traits characterized by greater routinization and lower risk-taking in earlier adult life.

Introduction

As early as 1913, a distinct personality type was described in patients with Parkinson's disease (PD) [1]. PD patients have been described as rigid, cautious and introverted [2]. It is biologically plausible that patients with PD may have differences in their personality due to the role of dopamine and the neurophysiology of the reward system of the brain. The dopaminergic nuclei of the brain stem are not only involved in the pathophysiology of motor symptoms [3], but influence personality as well [4]. Nevertheless, the evolution of the PD personality remains unclear and it is possible that personality differences noted in previous studies [5-9] represent changes that occurred at the same time or after the development of motor symptoms. Alternatively, the personality characteristics commonly associated with PD may represent long-standing traits and be detectable in early-adult life decades before initial motor symptoms. Previous studies suggest that premorbid personality characteristics may be associated with the risk of PD [5-10]. However, most of these studies utilized recall of subjective personality characteristics in early life, which may have been biased by the presence of the disease.

The objective of the present study was to determine to what extent activity- and lifestyle-based indicators of early-adult life personality correlate with personality characteristics typically seen in PD patients after diagnosis. If PD personality characteristics emerge along with motor symptoms of the disease, the correlations between these characteristics and early-life activities and lifestyle might be expected to differ between individuals with PD and those without this disease. Conversely, if both cases and controls show correlations in the same direction and magnitude, it would suggest that these indicators of

personality early in life represent stable personality characteristics, enabling them to be used as surrogate measures of early personality characteristics.

Methods

Population sampled

The Parkinson's Disease and Movement Disorders Center North Campus (PDMDC) at the University of South Florida (USF) is recognized as a Center of Excellence, serving over 5,000 patients in West Central Florida. Potential cases were identified through chart review of all patients who visited the PDMDC between January 1, 2007 and May 1, 2010. All cases whose charts indicated they met eligibility criteria were mailed recruitment materials. Potential controls were identified through a list of all patients age 50-80 years who visited the Family Practice clinics at USF between January 1, 2007 and December 31, 2007. From this list, each individual was assigned a random number [11], generating a unique pseudo-random value between 0 and 1 for each entry. Recruitment materials were mailed to individuals in sequential order in batches of 50 until the end of the recruitment period (May 2010).

Inclusion/exclusion criteria

Subjects were deemed eligible for the study if they met the following criteria: 1) age 50-80 years, 2) no evidence of significant memory impairment, and 3) able to speak and read English. Cases also must have been diagnosed with PD within the past 10 years and had to fulfill UK brain bank criteria [12]. We further required cases to have no atypical features of PD (pyramidal tract or cerebellar signs, apraxia, supranuclear gaze palsy,

unresponsiveness to levodopa, prominent and early autonomic dysfunction, or history of exposure to toxic substances associated with parkinsonism), absence of a history of surgical interventions for PD and lack of severe motor fluctuations (>50% of the day with dyskinesia or “off” time).

PD is more prevalent in Caucasians than in Asians and Blacks [13, 14] and racial differences in several domains of the Five Factor Model (NEO FFI) have been reported [15, 16]. Because of these potential differences and the underrepresentation of minorities in the PDMDC, the study was restricted to Caucasians, resulting in the exclusion of 3 Asians and 5 Blacks.

The protocol and questionnaires were approved by the USF Institutional Review Board, and all subjects gave written informed consent.

Procedures

Potential participants were contacted by telephone 4-5 days after the initial mailing to screen and recruit them for the study. Five attempts were made to contact each potential subject including at least one week day, one evening and one weekend call.

Exposure ascertainment

Study assessments were completed in a private setting at the medical clinic. Trained interviewers used highly structured questionnaires to complete in-person assessments. Assessments included measures of current personality, early- adult life personality

indicators and covariates. Names and scaling information for all personality variables are summarized in Table 2.1.

Current Personality Measures

Five-Factor Model (NEO FFI)

The NEO [14] identifies five broad dimensions of personality: openness, conscientiousness, extraversion, agreeableness and neuroticism (Table 2.1). Scores for these traits follow a continuum between the two extremes that define the trait, with a score of 1 representing the lower extreme and 5 representing the higher extreme.

Temperament and Character Inventory (TCI)

The TCI is based on Cloninger's psychobiological theory of personality and establishes differences between people with respect to seven dimensions of temperament and character [17]. The four temperament scales, described in Table 2.1, include novelty-seeking, harm-avoidance, reward dependence and persistence. The three character scales assess self-directedness, cooperativeness, and self-transcendence. Each item is rated as true or false by the subject. Answers reflecting a quality associated with a particular character or trait contribute 1 point toward the subscale score for that character or trait (some items are reverse-scored). Higher scores on a domain indicate greater presence of the temperament or character quality.

Premorbid Personality Indicators: Risk-taking and Routinization

Indicators of premorbid personality included three questionnaires developed by members of the study team (KLS, ARB and JAM) asking about routinized lifestyles and risk-taking behaviors.

Routinization

Early-adult routinization (e-Appendix 1) asked subjects about the regularity of their meal times and preferences for doing the same activities each day. Subjects were given choices on a Likert scale (always, usually, sometimes, seldom or never) to indicate how well 13 statements described them between the ages of 20-35 years. After completing this questionnaire, subjects were asked to report their current behaviors related to these activities. Responses were coded 0-4 with 0 assigned to the least routinized option and 4 assigned to the most routinized option (see score key in e-Appendix 1). The total score for this instrument was obtained by summing the score for the 13 items; the minimum possible score was 0 (not routinized) and the maximum possible was 52 (highly routinized). Cronbach's alpha for this scale was 0.74.

Risky Activities (RA) Questionnaire

The Risky Activity Questionnaire assessed participation in 10 risky activities (e-Appendix 2), including whether the subject had ever parachuted out of an airplane, ridden a motorcycle or a roller coaster, swum far from shore, gambled for large or small sums of money, parasailed, skied, or flew in a small plane. If a subject indicated they had participated in an activity, they were asked their age at the time of participation ("before

35", "after 35" and "both ages") and if they enjoyed the activity ("not at all", "sort of", "moderately", and "very much"). In order to assess the desire to engage in activities in the absence of the opportunity to actually have engaged in it, subjects were asked if they ever wanted to do each activity in which they had not participated. This questionnaire resulted in two scores representing risk-taking and sensation-seeking. To obtain the risk-taking score, one point was scored for each activity in which the subject participated for each time period or in which the subject did not participate in, but wanted to. The minimum possible risk-taking score was 0 points (no risky activities) and the maximum possible risk-taking score was 10 points (10 risky activities). The sensation-seeking score was based on the greatest level of enjoyment reported for any item on the questionnaire and ranged from 0 (no risky activities or activities were enjoyed "not at all") to 3 (enjoyed at least 1 activity "very much").

Risky Behavior (RB) Questionnaire

Subjects were asked to select the most accurate description of themselves from a group of statements related to five specific situations or behaviors: speeding when driving, flying in airplanes, getting lost in familiar and unfamiliar places, being in a high place, and wearing seatbelts in addition to a general summation of their enjoyment of risky situations (e-Appendix 3). Response choices included options without risk (0 points) as well as 2-3 options with increasing amounts of risk. Greater levels of risk scored more highly. Points for these 6 questions were summed to obtain the total score for this instrument with possible scores ranging from 0 points (behaviors with no risk or minimal risk) to 15 points (most risky behaviors).

Other Covariates

Other variables obtained included age at time of assessment; sex; years of education; smoking history including if subjects ever smoked cigarettes on a regular basis, the usual number of cigarettes smoked per day and the age smoking began and ended; and history of alcohol consumption including if subjects ever drank alcohol on a regular basis (defined as routinely drinking one or more alcoholic beverages per month), the number of servings of wine, beer and liquor consumed and the age each type of alcohol consumption started and ended. Major changes in alcohol consumption were captured by asking subjects if they ever regularly consumed more alcohol than initially reported and, if so, data for this period of consumption were also recorded. Smoking and alcohol data were converted into pack-years and drink-years to calculate total lifetime exposures. The age and sex of eligible cases and controls who refused study participation were abstracted from medical records.

Statistical Methods

Descriptive Statistics

Descriptive statistics were obtained for all independent variables, including means and standard deviations for continuous variables and frequency distributions for categorical variables. T-tests were used to compare cases and controls for continuous variables (age, years of education, pack-years of smoking, alcohol consumption) and chi-square for categorical variables (sex). Differences between participants and those who refused

participation were examined using t-tests for continuous variables and contingency table analysis (chi-square) for categorical variables.

Exploratory Factor Analysis of Routinization Instrument

To evaluate the structure of the routinization instrument, a principal components factor analysis was conducted among the controls for two versions (one applicable to ages 20-35; the other (not shown) applicable to preferences at the time the questionnaire was administered). For both versions, two factors were retained with eigenvalues greater than 1.0 (Table 2.2). One of these corresponded to a desire to maintain a routine and was labeled as "routinization." The other corresponded to a desire for experiences influenced by external factors and was labeled "externally-influenced experiences." Weighted item scores for these two factors were summed to obtain the subject's scores for each factor. Two items from the original instrument were not retained based on factor analysis. "I like to watch new shows or films on television" was dropped because it did not load on either of the retained components and did not fit conceptually with the other items in either component. When factor loadings among cases and controls were examined separately, "I like when things happen spontaneously" loaded on different components for cases and controls and was not retained.

Construction of Latent Variables for Personality

Principal components factor analysis was conducted among controls with scores for routinization, externally-influenced experiences, sensation-seeking, Risky Activities, Risky Behavior, smoking and alcohol consumption (in pack-years and drink-years).

These analyses were performed on data for ages 20-35 and the current period and factors with eigenvalues of 1.0 or higher were identified. The item representing “externally-influenced experiences” was not retained because it did not load on any of the retained components and did not fit conceptually with the other items in each component. A varimax rotation was performed after the item selection was finalized in order to reduce collinearity.

Separate data for ages 20-35 and the current period resulted in 2 sets of loadings. Although the loadings for each period were in the same direction and general magnitude, they were not identical and the loadings for ages 20-35 and the current period were averaged for each item. The averaged loading was used to weight the standardized value of each item. The weighted item scores were then summed to obtain the value for each latent variable which was used in subsequent analyses.

Potential Confounders

Age [18-20] and sex [18, 21] are risk factors for PD, and their associations with personality were therefore tested. Education also was considered as a potential confounder.

Logistic Regression Analysis

The association of current personality items with the risk of PD was assessed through logistic regression analyses adjusted for age, sex and education. Separate models were

constructed for each personality characteristic. P values of less than 0.05 (2-sided probability) were interpreted as being statistically significant.

Correlation of Premorbid Personality Indicators with Current Personality Characteristics

Pearson correlation coefficients were calculated to examine the association of early-adult life personality indicators with current personality traits in cases and controls separately, with the effects of age, sex and education partialed out. All analyses used SAS version 9.2 [22].

Results

Figure 2.1 summarizes participation among cases and controls. For cases, 1,228 charts were reviewed; 1,061 were considered ineligible and 167 were eligible and mailed recruitment materials. The first reason for ineligibility was noted and included: diagnosis other than PD (n=568), age less than 50 years (n=154), age greater than 80 years (n=114), atypical parkinsonism (n=75), PD diagnosed more than 10 years (n=65), surgical intervention for PD (n=33), cognitive impairment (n=29), severe motor fluctuations (n=8), race (n=8), unable to complete study assessments (n=2 who did not speak English), departed study area (n=1), and deceased (n=4). Telephone calls were made to these 167 potential cases and 138 were successfully contacted. Upon further assessment of eligibility by telephone, 13 cases were found to be ineligible [atypical parkinsonism (n=1), unable to speak English (n=2), cognitive impairment (n=2), deceased (n=1), PD diagnosed more than 10 years ago (n=3), diagnosis other than PD (n=1), surgical

intervention for PD (n=2), and departed study area (n=1)]. Fifty-five of the remaining 125 potential cases refused participation and 70 completed study interviews. The participation rate among eligible cases was 70/125 (56%).

In addition to the cases recruited from the PDMDC, cases were recruited from two outlying neurology clinics in order to increase the sample size. Eighty-eight patients from these clinics were contacted; 56 were ineligible due to diagnosis other than PD (n=11), age less than 50 years (n=1), age greater than 80 years (n=20), atypical parkinsonism (n=5), PD diagnosed more than 10 years (n=4), surgical intervention for PD (n=10), cognitive impairment (n=1), severe motor fluctuations (n=1), race (n=2), and unable to complete study assessments (n=1 who was blind). Thirteen potential subjects from these sites refused participation and 19 participated.

The computer-generated list of eligible controls included 5,158 individuals. Letters were mailed to 349 potential controls and 224 were successfully contacted by telephone. Upon further assessment of eligibility, 17 controls were found to be ineligible [inability to speak English (n=6), deceased (n=5), race (n=4), atypical parkinsonism (n=1), and cognitive impairment (n=1)]. One hundred and eight of the remaining 207 potential cases refused participation and 99 completed study interviews. The participation rate among eligible controls was 99/207 (48%). Demographic characteristics of individuals who participated in the study were compared to those who refused participation (Table 2.3). For both cases and controls, there were no significant differences in age or sex between those who participated and those who refused.

Demographic and current personality characteristics of the study sample are shown in Table 2.4. There was a higher proportion of men among cases (65%) compared with controls (44%, p=0.005). In addition, cases had fewer total years of education compared with controls (14.81 ± 3.10 years compared with 16.26 ± 3.54 years, p=0.003). The crude ORs (unadjusted) for ever-smoking (OR=0.88 (95% CI 0.50-1.57)) and ever-drinking alcohol (OR=1.30 (95% CI 0.60-2.83)) did not differ significantly between cases and controls.

Factor Analysis of Early-Adult Life Personality Indicators

Three factors were retained in the factor analysis of Risky Activities, Risky Behaviors, routinization, sensation-seeking, lifetime smoking and alcohol consumption (Table 2.5). The grouping of items into the three factors represented three latent constructs: routinization, lifestyle risks (smoking and alcohol consumption) and activity risks (Risky Activities and Risky Behaviors).

Current Personality

Personality dimensions assessed by the NEO-FFI demonstrated that higher levels of neuroticism were associated with having PD (OR=1.05 (95% CI 1.00-1.11)) adjusting for age, sex and education (Table 2.6). PD was also associated with higher levels of harm-avoidance (OR=1.07 (95% CI 1.00-1.15)). There were no significant associations between PD and other NEO or TCI measures.

Association of Early Personality Indicators and Current Personality

Consistent patterns of significant correlations were observed among both cases and controls for early-adult life routinization with current measures of neuroticism (cases: r=0.33, p=0.01; controls: r=0.26, p=0.04), extraversion (cases: r=-0.33, p=0.01; controls: r=-0.33, p=0.04), novelty-seeking (cases: r=-0.33, p=0.01; controls: r=-0.34, p=0.007), harm-avoidance (cases: r=0.47, p=0.0003; controls: r=0.45, p=0.0002) and for the association of early-adult life activity risks with harm- avoidance (cases: r=-0.47, p=0.0004; controls: r=-0.42, p=0.0006) (Table 2.7).

Discussion

We found that PD cases had higher current levels of neuroticism and harm-avoidance than controls. Current personality characteristics were associated with indicators of early-adult personality, including taking activity risks and routinization in both cases and controls.

Case-control studies have found differences in current personality characteristics, including reduced sensation-seeking [23], reduced novelty-seeking [24, 25] and higher harm-avoidance [24, 26] in cases with PD compared to normal [23, 24] and medical [25, 26] controls. Fujii [24] found that the mean novelty-seeking score among cases was significantly reduced compared with controls (mean ± SD = 12.36 ± 3.02 among cases and 13.71 ± 3.15 among controls, p<0.05) while harm-avoidance was significantly greater among cases (mean=19.94 ± 5.14) compared with controls (mean=15.73 ± 6.49)

(p<0.001). However, cases were administered the test via interview, while controls completed a paper version of the questionnaire; this difference in mode of administration could have biased the results away from the null. In our study, novelty-seeking was not associated with PD. The different findings in previous studies of reduced novelty-seeking among individuals with PD [6, 25] and our null finding may be attributable to a change in patterns of treatment for PD over time. Both of the previous studies were conducted prior to the approval of the dopamine agonists (DAs) pramipexole and ropinirole for the treatment of PD in 1997. Since that time, DAs have become first-line treatments for PD [27, 28]. DAs have been shown to significantly increase novelty-seeking in previously unmedicated patients with PD, while harm-avoidance remained unchanged [29]. In the present study, 83 cases (93%) were taking dopamine agonists for PD with 46% taking ropinirole or pramipexole. None of the controls reported taking either medication.

Findings similar to our observations of increased neuroticism and harm-avoidance have been reported previously. A historical cohort study of 7,216 subjects in Rochester, Minnesota evaluated measures from the Minnesota Multiphasic Personality Inventory (MMPI) and found that increased neuroticism as a younger adult was associated with higher PD risk (HR=1.54; 95% CI 1.10-2.16) [30]. In a study of 122 young, unmedicated patients with PD, Jacobs et al [31] reported higher levels of harm-avoidance (mean ± SD = 17.8 ± 5.7) compared with age- and sex-matched controls (12.1 ± 4.9).

Dopaminergic activity has been reported as the primary influence on harm-avoidance [32] and has been correlated with decreased ^{18}F-dopa uptake in the right caudate nucleus

(r=0.53, *p*=0.04) [26]. Differences in novelty-seeking and harm-avoidance in individuals with PD compared with controls have been reported to depend on the brain hemisphere where dopamine loss was most pronounced [33] with reduced novelty-seeking associated with left-hemisphere dopamine deficiency and increased harm avoidance associated with right-hemisphere dopamine deficiency.

Personality traits are highly stable during adulthood [34-36], although there is evidence for a "maturation effect" [37]. We found a stable association between activity risks in early- adult life and harm-avoidance as well as between early routinization preference and novelty-seeking, both of which may be related to dopaminergic function [38]. This stability was present not only among controls but also among cases, which supports the hypothesis that behaviors associated with the PD personality may exist many years before the presentation of motor symptoms.

This study had several strengths. The assessments were unique in that they used activities and lifestyle patterns as retrospective indicators of personality traits. Previous studies of premorbid personality traits have employed the subject's own assessment of personality traits that may be more likely to be affected by recall bias and are generally subjective in nature. Another strength was the selection of medical controls, which reduces the potential for selection bias related to factors associated with the probability of seeking medical care (such as socioeconomic status) and of being diagnosed with PD if symptoms are present.

Our study is limited by the retrospective assessment of early-adult life indicators related to personality. The possibility that recall of activities, behaviors and preferences in early-adult life may be influenced by current personality cannot be excluded. However, the fact that similar correlations were seen among both cases and controls suggests that the presence of PD symptoms are likely not responsible for the associations found.

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Chapter 2 Tables

Table 2.1: Current personality measures and early-adult life personality indicators

Variable	Description	Instrument of Origin	Scoring procedure	Score (range)
Openness	Inventive and curious rather than cautious	NEO	Sum of items in domain (scoring key included with instrument); higher scores indicate more inventive and curious personality; lower scores indicate cautious personality	10-50
Conscientiousness	Efficient and organized rather than easy-going and careless	NEO	Sum of items in domain (scoring key included with instrument); higher scores indicate more efficient and organized personality; lower scores indicate easy-going and careless personality	12-60
Extraversion	Outgoing and energetic rather than shy and reserved	NEO	Sum of items in domain (scoring key included with instrument); higher scores indicate more outgoing and energetic personality; lower scores indicate shy and reserved personality	12-60
Agreeableness	Friendly and compassionate rather than cold and unkind	NEO	Sum of items in domain (scoring key included with instrument); higher scores indicate more friendly and compassionate personality; lower scores indicate cold and unkind personality	12-60
Neuroticism	Sensitive and nervous rather than secure and confident	NEO	Sum of items in domain (scoring key included with instrument); higher scores indicate more sensitive and nervous personality; lower scores indicate secure and confident personality	12-60
Novelty-seeking	Easily angered, curious, easily bored, impulsive, extravagant, and disorderly	TCI	Sum of items in domain (scoring key included with instrument); Higher scores indicate greater presence of the temperament	0-20
Harm-avoidance	Exhibited as fear, inhibition of behavior in response to punishment or non-reward, and pessimism	TCI	Sum of items in domain (scoring key included with instrument); Higher scores indicate greater presence of the temperament	0-20
Reward- dependence	Attachment, sentimentality, social sensitivity, and dependence on approval by others	TCI	Sum of items in domain (scoring key included with instrument); Higher scores indicate greater presence of the temperament	0-15
Persistence	Ambition, industriousness, determination, and perfectionism	TCI	Sum of items in domain (scoring key included with instrument); Higher scores indicate greater presence of the temperament	0-5

Table 2.1 (Cont)

Variable	Description	Instrument of Origin	Scoring procedure	Score (range)
Self-directedness	Responsible, reliable, resourceful, goal-oriented, and self-confident	TCI	Sum of items in domain (scoring key included with instrument); Higher scores indicate greater presence of the character	0-25
Cooperativeness	Perception of oneself as part of society; empathetic, tolerant, and compassionate	TCI	Sum of items in domain (scoring key included with instrument); Higher scores indicate greater presence of the character	0-25
Self-transcendence	Perception of oneself as part of the universe as a whole; spiritual, unpretentious, humble and fulfilled	TCI	Sum of items in domain (scoring key included with instrument); Higher scores indicate greater presence of the character	0-15
Early-Adult Routinization	Preference for regularity in daily activities and routines ages 20-35 years	Routinization instrument (see e-Appendix 1)	Sum of item scores (see e-Appendix 1); Factor score obtained through factor analysis	0.10-0.56*
Early-Adult Activity risks	Engagement in risky activities ages 20-35 years	Risk taking instruments (see e-Appendix 2 and e-Appendix 3)	Sum of item scores (see e-Appendix 2 and e-Appendix 3); Factor score obtained through factor analysis	0.65-3.77*
Early-Adult Lifestyle Risks	Engagement in risky behaviors (smoking cigarettes and drinking alcohol) ages 20-35 years	Smoking and drinking histories (pack-years and drink-years)	Sum of pack-years and drink-years; Factor score obtained through factor analysis	0.53-3.08*

* range after standardization of component item scores and calculation of latent variable

Table 2.2: Routinization factor loadings (based on controls)

Item	Factor 1 (Routinization)	Factor 2 (Externally influenced experiences)
Average loadings (Early adult and current)		
In general, I like(d) to do the same things each day.	0.59	0.06
I like(d) to wake up and go to bed at the same time each day.	0.55	-0.12
I like(d) to eat my meals at the same time each day.	0.72	-0.15
I like(d) to try new or different foods.	0.14	0.71
I usually sit/sat in the same seat when doing certain activities (for example: reading, watching TV, eating).	0.65	-0.12
I usually put personal objects back in the same place each time I use(d) them.	0.40	-0.27
I like(d) to plan my days out in advance.	0.42	-0.50
Other people think/thought I am/was “set in my ways”.	0.67	-0.08
I think I am/was “set in my ways”.	0.74	-0.12
I like(d) to meet new people.	0.32	0.76
I like(d) to try new things that I’ve never done before.	0.46	0.74

Table 2.3: Comparison of Participants and Refusals

		Participants (cases n=89; controls n=99)	**Refusals (cases n=68; controls n=108)**	***p*-value**
Age, in years [a]	Cases	68.47 ± 8.00	68.46 ± 7.65	0.99
	Controls	67.31 ± 6.96	66.64 ± 7.50	0.50
Sex (% male)	Cases	65.17	55.88	0.24
	Controls	44.44	45.37	0.89

[a] mean ± sd (range)

Table 2.4: Demographic and personality characteristics of 89 cases and 99 controls: means, standard deviations and ranges (where applicable)

	Cases			Controls		
	Total (N=89)	**Men (N=58)**	**Women (N=31)**	**Total (N=99)**	**Men (N=44)**	**Women (N=55)**
Age, in years[a]	68.47 ± 8.00 (50–80)	68.74 ± 8.10 (50-80)	67.97 ± 7.91 (51-79)	67.31 ± 6.96 (50–80)	69.05 ± 6.44 (55-80)	65.93 ± 7.11 (50-79)
Sex (% male)	65.17[*]	n/a	n/a	44.44[*]	n/a	n/a
Smoking (% ever smoked)	49.44	53.45	41.94	52.53	63.64	43.64
Alcohol (% ever drank)	85.39	91.38	74.19	81.82	86.36	78.18
Education – highest grade completed[a]	14.81 ± 3.10 (8–24)[*]	15.21 ± 3.07 (8-24)	14.06 ± 3.08 (9-23)[*]	16.26 ± 3.54 (9–24)[*]	16.20 ± 3.41 (11-24)	16.31 ± 3.67 (9-24)[*]

[a] mean ± sd (range)

[*] $p<0.05$ cases compared to controls (crude)

Table 2.5: Early-adult personality item factor loadings (based on controls)

Item	Factor 1 (Activity risks)	Factor 2 (Lifestyle risks)	Factor 3 (Routinization)
	Average loadings (Early adult and current)		
Routinization score	-0.03	0.04	0.93
Risky Behavior score	0.55	0.05	-0.53
Risky Activities: risk taking score	0.81	0.12	-0.02
Risky Activities: sensation seeking score	0.81	-0.02	-0.07
Smoking (pack-years)	0.06	0.78	-0.13
Alcohol consumption (drink-years)	0.01	0.83	0.14

Table 2.6: Association of current personality traits with PD [OR (95%CI)]

Effect	Unadjusted model	Adjusted model[a]
Neuroticism[b]	1.04 (1.00-1.09)	1.05 (1.00-1.11) *
Extraversion[b]	0.99 (0.94-1.04)	1.00 (0.95-1.06)
Openness[b]	0.94 (0.89-0.98)*	0.98 (0.91-1.05)
Agreeableness[b]	0.99 (0.93-1.05)	1.03 (0.96-1.10)
Conscientiousness[b]	0.96 (0.91-1.01)	0.96 (0.91-1.01)
Novelty-seeking[c]	1.08 (0.98-1.19)	1.09 (0.99-1.21)
Harm-avoidance[c]	1.05 (0.99-1.12)	1.07 (1.00-1.15) *
Reward dependence[c]	0.95 (0.86-1.05)	0.96 (0.86-1.07)
Persistence[c]	1.07 (0.88-1.29)	1.09 (0.88-1.34)
Self-directiveness[c]	0.91 (0.83-0.99) *	0.92 (0.84-1.01)
Cooperativeness[c]	0.86 (0.76-0.98)	0.89 (0.78-1.02)
Self-transcendence[c]	0.97 (0.91-1.05)	0.96 (0.89-1.04)

[a] Adjusted for age, sex and education
[b] Current traits as measured by NEO
[c] Current traits as measured by TCI
* $p<0.05$

Table 2.7: Partial correlation coefficients for early-adult indicators and current personality measures

Current Personality Measure		**Activity risks†**	**Lifestyle risks†**	**Routinization†**
Neuroticism	Cases	-0.33*	-0.11	0.33*
	Controls	-0.15	-0.07	0.26*
Extraversion	Cases	0.24	-0.03	-0.33*
	Controls	0.37*	0.02	-0.33*
Openness	Cases	-0.02	-0.16	-0.01
	Controls	0.26*	0.08	-0.33*
Agreeableness	Cases	-0.09	-0.06	0.19
	Controls	-0.15	-0.20	-0.01
Conscientiousness	Cases	0.03	0.27	0.15
	Controls	0.20	0.03	-0.02
Novelty- seeking	Cases	0.23	0.07	-0.33*
	Controls	0.21	0.08	-0.34*
Harm-avoidance	Cases	-0.47*	-0.15	0.47*
	Controls	-0.42*	-0.08	0.45*
Reward dependence	Cases	-0.25	-0.21	0.14
	Controls	0.12	-0.19	0.03
Persistence	Cases	-0.01	0.02	0.09
	Controls	0.07	0.07	-0.06
Self- directiveness	Cases	0.17	0.11	-0.01
	Controls	0.14	0.15	0.03
Cooperativeness	Cases	-0.12	0.17	0.12
	Controls	0.11	-0.11	-0.13
Self -transcendence	Cases	-0.04	0.05	-0.04
	Controls	0.04	-0.22	-0.02

† adjusted for age, sex and education
* $p<0.05$

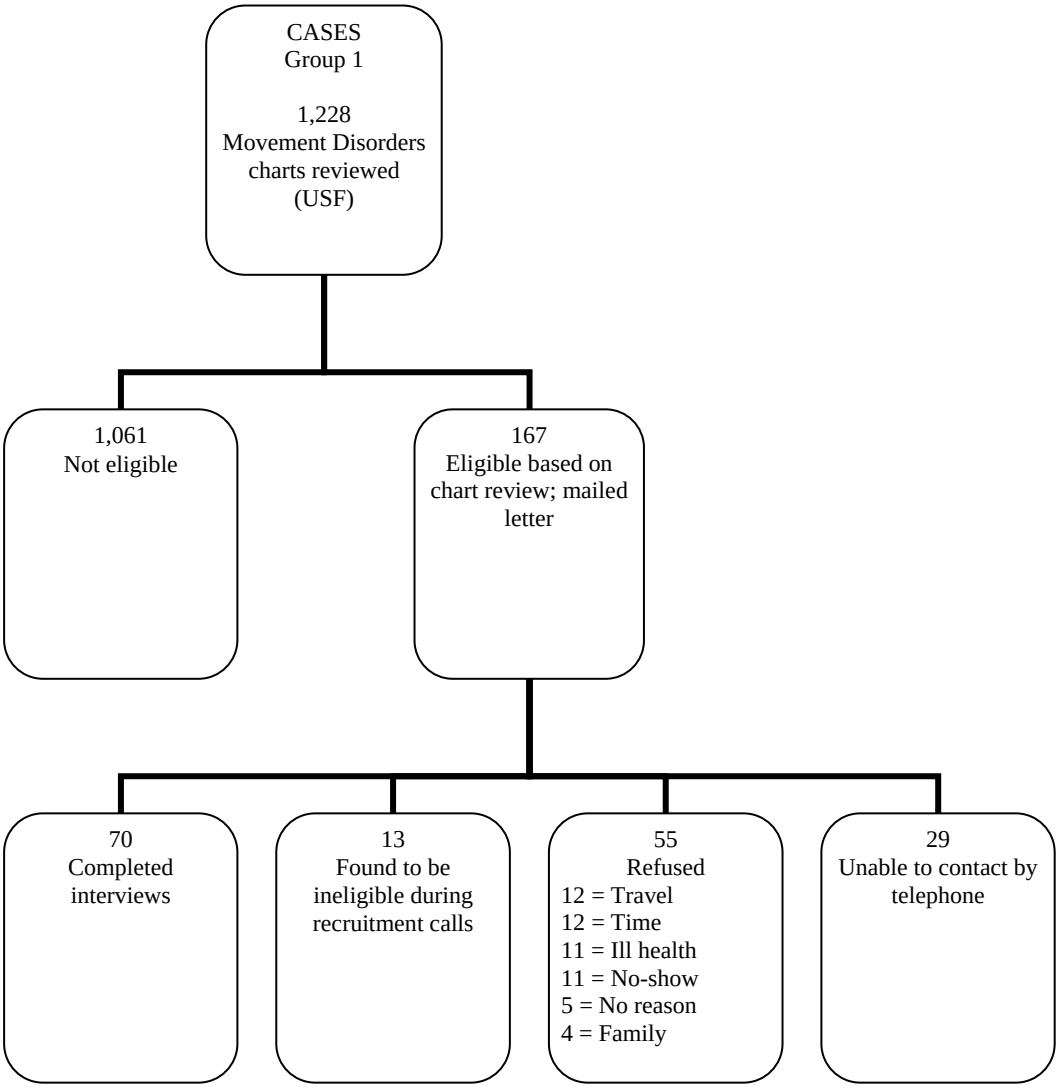

Figure 2.1: Participation among cases and controls

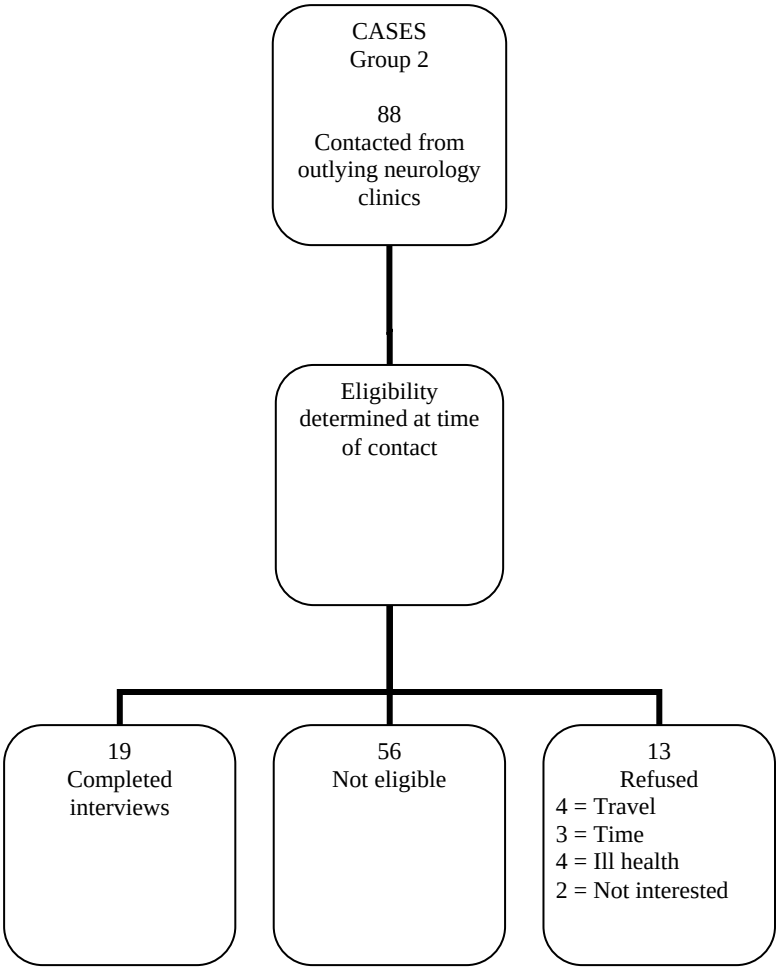

Figure 2.1 (Cont)

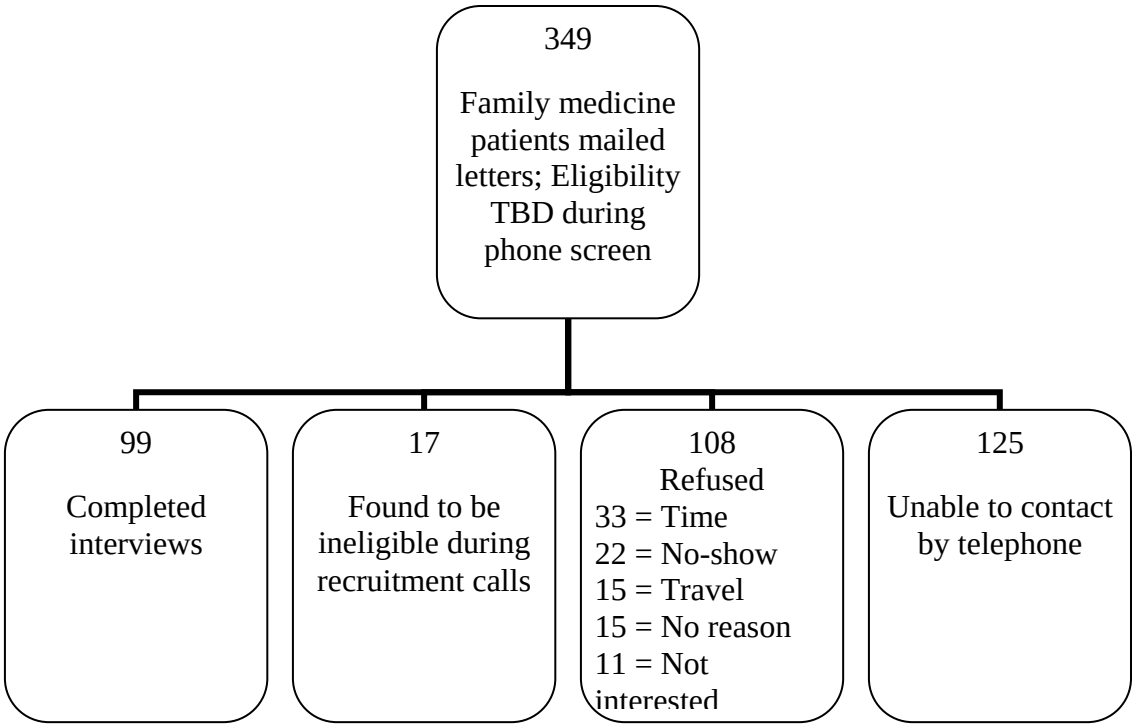

Figure 2.1 (Cont)

e-**Appendix 1: Early-Adult Routinization Instrument**

Think back to when you were a young adult (age 20-35 years).
Please mark the box that best matches how well each statement describes you at that time.

		Always	**Usually**	**Some-times**	**Seldom**	**Never**
1	In general, I liked to do the same things each day.					
2	I liked to watch new shows or films on television.					
3	I liked to wake up and go to bed at the same time each day.					
4	I liked to eat my meals at the same time each day.					
5	I liked to try new or different foods.					
6	I usually sat in the same seat when doing certain activities (for example: reading, watching TV, eating).					
7	I usually put personal objects back in the same place each time I used them.					
8	I liked to plan my days out in advance.					
9	I liked when things happen spontaneously.					
10	Other people thought I was “set in my ways”.					
11	I think I was “set in my ways”.					
12	I liked to meet new people.					
13	I liked to try new things that I’d never done before.					

Scoring:
Items 1, 3, 4, 6, 7, 8, 10, 11: Always=4, Usually=3, Sometimes=2, Seldom=1, Never=0
Items 2, 5, 9, 12, 13: Always=0, Usually=1, Sometimes=2, Seldom=3, Never=4
Total score = Sum of score for items 1-13

e-**Appendix 2: Risky Activities Questionnaire**

Have you:			**If No:**			**If Yes:**					
1. Ridden on a large roller-coaster three or more times?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9
Have you:			**If No:**			**If Yes:**					
2. Gambled for moderate to large sums of money three or more times?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9
Have you:			**If No:**			**If Yes:**					
3. Gambled for small sums of money three of more times?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9
Have you:			**If No:**			**If Yes:**					
4. Parachuted out of an airplane?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9

e-Appendix 2 (Cont)

Have you:			**If No:**			**If Yes:**					
5. Parasailed (a parachute pulled by a boat)?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9
Have you:			**If No:**			**If Yes:**					
6. Downhill skied three or more times?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9
Have you:			**If No:**			**If Yes:**					
7. Water skied three or more times?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9
Have you:			**If No:**			**If Yes:**					
8. Swam far from shore or in very heavy surf?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9

e-Appendix 2 (Cont)

Have you:			**If No:**			**If Yes:**					
9. Driven or ridden on a motorcycle?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9
Have you:			**If No:**			**If Yes:**					
10. Flown in a small private plane?	No	0	Is this something you ever wanted to do?	No	0	Did you enjoy this activity?	Not at all	1	At what age did you do this?	Before 35	0
	Yes	1		Maybe, not sure	1		Sort of	2		After 35	1
	DK	-9		Yes	2		Moderately	3		Both ages	2
				DK	-9		Very much	4		DK	-9

Scoring:

Risk taking score: 1 point for each item where participation = “yes” OR where “Is this something you ever wanted to do?” = “yes”

For early adulthood, responses with “Before 35” or “Both ages” were used to calculate the score. For later adulthood, only responses with “After 35” or “Both ages” were used to calculate the score.

Sensation-seeking score:

3 points if at least 1 activity was enjoyed “very much”
2 points if at least 1 activity was enjoyed “moderately” but none greater
1 point if at least 1 activity was enjoyed “sort of” but none greater
0 points if activities were enjoyed “not at all” or if no activities were undertaken

e-**Appendix 3: Risky Behaviors Questionnaire**

For each question, please check the statement that describes you best by placing a check mark (✓) in the appropriate box.			
	Check one of the boxes below: ➔	✓	*For office use*
1. During most of my life:	I liked to drive considerably faster than the speed limit.		3
	I liked to drive at or close to the speed limit.		2
	I liked to drive below the speed limit.		1
	I never drove a car.		0

	Check one of the boxes below: ➔	✓	*For office use*
2. During most of my life:	I enjoyed the experience of flying in airplanes very much.		3
	I felt indifferent about flying in airplanes.		2
	I only flew in airplanes if I had to.		1
	I never flew in an airplane.		0

e-Appendix 3 (Cont)

	Check one of the boxes below: ➔	✓	*For office use*
3. During most of my life, when I traveled to a place I didn't know:	I preferred to go where I wished without planning, even if it meant getting lost.		2
	I preferred to plan most, but not all, of my trip in advance.		1
	I preferred to know exactly where I would be most of the time and how I would get there.		0

	Check one of the boxes below: ➔	✓	*For office use*
4. During most of my life, I found being in a high place, such as a building or mountain:	An exciting and enjoyable experience.		2
	Made me feel somewhat uncomfortable.		1
	Scared me a great deal		0

	Check one of the boxes below: ➔	✓	*For office use*
5. Since the time that seat belts have been routinely installed in cars (around 1980), when I am in a car:	I never wear my seat belt.		3
	I usually do not wear my seat belt.		2
	I usually wear my seat belt.		1
	I always wear my seat belt.		0

e-Appendix 3 (Cont)

Please check the statement below that BEST describes you.		
Check one of the boxes below: ➔	✓	*For office use*
6. During most of my life, I found dangerous or risky situations exhilarating and was willing to give up some control for the thrill.		2
During most of my life, I found some danger or risk exciting, but only if I had control of the situation.		1
During most of my life, I have avoided risky situations, because I believe that it is better to be safe than sorry.		0

Scoring: Sum points for all items

Chapter 3

Premorbid Personality and the Risk of Parkinson's Disease

Abstract

Background: Previous studies support the hypothesis that premorbid personality characteristics may be associated with the risk of Parkinson's disease. However, most of these relied upon subjective reports of premorbid personality earlier in life, which may be subject to recall bias.

Objective: To evaluate the association of PD with risk-taking, routinization, smoking and alcohol consumption in early-adult life as indicators of premorbid personality.

Methods: In-person interviews were conducted with 89 Parkinson's disease patients and 99 controls from a university-based medical center. Associations between indicators of early-adult personality and risk of Parkinson's disease were examined using logistic regression.

Results: Adjusting for age, sex and education, taking or wanting to take more activity risks as a young adult was inversely associated with the risk of Parkinson's disease in the entire sample (OR=0.78 (95% CI 0.63-0.97)). Among women, higher levels of routinization as a young adult were associated with an increased risk of Parkinson's disease (OR=1.63 (95% CI 1.05-2.53)).

Conclusions: Parkinson patients were more likely to take or want to take fewer risks in early-adult life and to prefer a more routine lifestyle than controls, suggesting that

individuals with Parkinson’s disease may have distinctive premorbid personality characteristics.

Introduction

In the companion paper [1], we showed that engagement or desired engagement in risky activities before the age of 35 was positively correlated with current levels of novelty-seeking and inversely correlated with current levels of harm-avoidance in cases as well as in controls. Likewise, young-adult routinization was inversely correlated with novelty-seeking and positively correlated with harm-avoidance in both cases and controls. These findings indicate the stability of personality traits in PD and support their assessment as possible non-motor indicators of the disease.

Case-control studies examining premorbid personality have found that PD patients had reduced leadership tendencies, flexibility and sociability and were more quiet, generous, cautious, introverted, rigid, socially conforming and even-tempered during the time period prior to the onset of PD compared with controls [2-8]. However, other studies failed to find an association between premorbid personality measures and PD [9, 10]. Many of the previous studies were limited by small sample size [2, 3, 5-7, 10-12], use of proxies to report personality [3, 10] and potential for recall bias resulting from the use of subjective personality assessments in prevalent cases [2-7, 10-15]. The objective of the current study was to evaluate the association of premorbid personality indicators in earlier adult life, including participation or desired participation in risky activities, preference for a routine lifestyle, and cigarette and alcohol consumption, with the risk of PD.

Methods

Subjects

Subject selection and participation have been fully detailed previously [1]. Briefly, cases were recruited from a Movement Disorders clinic and controls from a Family Medicine clinic at the University of South Florida. Potential subjects were contacted by mail and then by telephone to screen and recruit them. Eligibility criteria required subjects to be aged 50-80 years, Caucasian, free from memory impairment, and able to read and speak English. Cases were ineligible if they had a diagnosis of atypical PD, a history of neurosurgery for PD, or severe motor fluctuations. The protocol and questionnaires were approved by the University of South Florida's Institutional Review Board and all subjects gave written informed consent prior to the commencement of data collection.

Exposure assessments

Trained interviewers used highly-structured questionnaires to complete in-person assessment of subjects at the study site (medical clinic) in private settings. Indicators of premorbid personality included past risk-taking behaviors, routinization, smoking and alcohol consumption before age 35. These indicators were assessed with questionnaires developed by the study team and described in the companion article [1]. For logistic regression, the Odds Ratios and 95% Confidence Intervals for PD associated with smoking and alcohol consumption were constructed to reflect units of 10 pack-years of smoking and 10-year drink-years of alcohol consumption.

Covariates

Age, sex and years of formal education were also assessed during the study interview.

Statistical Methods

Factor loadings from a principal components factor analysis were used to create latent variables representing early-adult (less than age 35 years) risk-taking and routinization as previously described [1]. The association of early-adult life risk-taking activities, routinization and smoking and alcohol consumption with the risk of PD was assessed through unconditional logistic regression analysis, adjusted for age, sex and education. Because men and women might have had different opportunities to participate in certain activities, we also conducted analyses stratified by sex. P-values less than 0.05 (2-sided test) were interpreted as being statistically significant. All data were analyzed using SAS version 9.2 [16].

Results

Recruitment and participation details have been detailed in the companion article [1]. A total of 99 cases and 89 controls completed study assessments. Although there was no difference in mean age between cases and controls (p=0.29), there was a significantly greater proportion of men among cases (65.2% of cases vs. 44.4% of controls; p=0.005). Cases also completed approximately 1.5 fewer years of formal education than controls (p=0.003).

Characteristics of participants' early-adult personality and smoking and alcohol consumption are shown in Table 3.1. The proportion of subjects who had ever smoked cigarettes (49% of cases and 53% of controls) or drank alcohol (85% of cases and 82% of controls) did not differ between cases and controls (p=0.67 and p=0.51, respectively, [1]), nor did the number of pack-years (mean ± SD for cases = 10.86 ± 18.47 pack-years; mean for controls = 12.43 ± 23.09 pack-years; p=0.60) or drink-years (mean ± SD for cases = 61.35 ± 114.38 drink years; mean for controls = 46.78 ± 80.83 drink years; p=0.32). Significant differences were seen among women for both activity risks and preferences for more routinization as young adults.

In logistic regression analyses adjusted for age, sex and education, taking and wanting to take more activity risks as a young adult was inversely associated with the risk of PD in the total sample (OR=0.78 (95% CI 0.63-0.97)) and among women (OR=0.69 (95% CI 0.50-0.95)) (Table 3.2). The adjusted risk of PD among men who reported taking activity risks as a young adult was also reduced (OR=0.88 (95% CI 0.66-1.19)), but was not statistically significant. Among women but not men, a higher degree of routinization was associated with a higher risk of PD (OR=1.63 (95% CI 1.05-2.53)).

Neither history of ever-smoking (adjusted OR for total sample = 0.67 (95% CI 0.36-1.25)) nor pack-years of smoking was statistically associated with PD despite there being a trend toward an inverse association (OR=0.90 (95% CI 0.77-1.04)) adjusting for age, sex and education. No association was found between with alcohol use and risk for PD.

When activity risks, routinization, pack-years of smoking, drink-years of alcohol consumption, age, sex and education were entered in the model (Table 3.2), young adult risk-taking remained significantly associated with PD.

Discussion

In this study of 89 PD cases and 99 clinic-based controls, taking or wanting to take more risks as a young adult was associated with a decreased risk of PD in the entire sample and among women. Women who reported greater preference for routinization as a young adult were also at increased risk for PD. Neither pack-years of smoking nor drink-years of alcohol were statistically associated with risk of PD in our sample, but there was a trend for pack-years to be inversely associated. The significant association of risk-taking as a young adult with PD remained when other personality indicators were included in the model.

Relatively little information is available from previous studies on sex differences in personality or psychiatric conditions preceding onset of PD. In a historical cohort study [17] men with PD were more likely to be diagnosed or treated for depression or anxiety compared with controls [18] and to have a greater likelihood of anxiety [17], while there was no difference for depression or anxiety among women. However, a small case-control study found that women with PD have an increased risk of hypochondria, depression, hysteria and social introversion as measured by the MMPI while there were no psychiatric or personality differences among male cases compared with controls [11].

In contrast, Arabia's historical cohort study [9] found similar results in men and women on MMPI measures of sensation-seeking, hypomania and positive emotionality.

Previous epidemiologic studies, including several meta-analyses, have demonstrated that smoking, caffeine, and alcohol intake are inversely associated with the risk of PD [19-27]. Results from a pooled analysis of 2,328 cases and 4,113 controls [23] showed a lower risk of PD in ever-smokers (OR=0.70 (95% CI 0.63-0.78)). Our findings were consistent with the pooled case-control results with regard to the adjusted point estimate (OR for smoking history=0.67 (95% CI 0.36-1.25)); the lack of statistical significance in our smoking findings may be due to the relatively small sample size. Pack-years of smoking was lower in our sample among both cases (mean =10.86±18.47) and controls (mean= 12.43±23.09) compared with previous reports (range of mean values in previous studies = 16-46) [23]; the high educational level of our sample might account for this difference. Other meta-analyses have shown that smoking as well as caffeine and alcohol intake are inversely associated with PD risk [19-27] and it has been theorized that nicotine may be neuroprotective [28].Two explanations of the inverse association between smoking and PD must be considered: 1) smoking increases striatal dopamine transporter activity [29], increases levels of vesicular dopamine receptors [29], reduces the loss of dopaminergic neurons in the substantia nigra [30], and stimulates dopamine release [31-33], possibly through its inhibition of monoamine oxidase (MAO) [34-36] which catabolizes dopamine [37], and/or 2) the reward system of the brain may differ in individuals who are destined to develop PD, resulting in a reduction in voluntary exposure to smoking. Although our observations related to pack-years of smoking did

show significant differences, cases in our study reported fewer pack-years of smoking compared with controls and this difference was more pronounced among men. In the pooled analysis described above similar results were reported for men (OR=0.74 (95% CI 0.64-0.86)) and women (0.61 (0.51-0.72)) with regard to ever vs. never smoking [23]. These point estimates are comparable to our findings among men (OR=0.66 (0.29-1.50)) and women (OR=0.62 (0.23-1.68)), although our relatively small sample size likely resulted in wider confidence intervals precluding statistical significance.

Previous studies of premorbid personality in PD have yielded inconsistent results [2-10]. The validity of results from studies that rely on subjective retrospective measures of personality is questionable as this assessment may be limited by the potential for recall bias associated with having a chronic disease. To examine the temporal sequence of the association between risk-taking and PD and to exclude the possibility of recall bias in the evaluation of results, assessment of personality should be performed as distally as possible from the onset of PD and preferentially prospectively. The Mayo Clinic Cohort Study of Personality and Aging [9, 38] included 7,216 subjects from Olmsted County, Minnesota who completed the Minnesota Multiphasic Personality Inventory (MMPI) as young adults (aged 20-39 years). During a follow-up period with a median of 29.2 years, 156 subjects developed PD. The risk of PD was associated with increased neuroticism as a young adult (Hazard Ratio=1.54 (95% CI 1.10-2.16)) and higher scores in anxiety (HR=1.63 (95% CI 1.16-2.27)) [38]. There was no difference in levels of sensation-seeking, hypomania, positive emotionality, social introversion or constraint among subjects who developed PD compared to those who remained free from PD [9].

Another approach has been to study twins who are discordant for the disease [2, 5, 12] and to compare personality characteristics between affected and unaffected twins. Heberlein et al used a semi-structured interview to evaluate premorbid lifestyle and activities that may be influenced by subjects' personalities such as hobbies, education, friendship, and travel [2]. There were no differences in history of these activities, although the sample was small (n=15 twin pairs). Another study of twins discordant for PD reported that the twin with PD was less often in a leadership role, less aggressive, less confident, less light-hearted, and more nervous, quiet, and self-controlled compared to the twin without the disease, and these differences were present 10 years prior to the onset of PD [5]. In addition, twins with PD smoked significantly fewer cigarettes than their unaffected siblings [5]. Duvoisin et al [12] examined 12 twin pairs discordant for PD and reported indications of personality differences as early as adolescence, although these differences were not evaluated statistically.

An important strength of the current study was the use of activities and habits as indicators of premorbid personality. Although these evaluations were retrospective and also could be subject to recall bias, it is less likely that cases and controls would recall activities and habits differently due to influences of PD, compared to recall of premorbid personality characteristics. The small sample size was a limitation of this study and may have contributed to the failure to find differences that might have reached statistical significance in a larger sample (e.g., between ever-smoking and risk of PD).

The finding of an increased risk of PD among those with lower risk-taking tendencies in earlier adult life is consistent with association of this characteristic with harm-avoidance and neuroticism in later life [1], the most commonly reported features of the personality of Parkinson patients [13, 15, 38-40]. The present findings suggest that personality characteristics in earlier life manifested by fewer risk-taking behaviors and preferences for a predictable routine lifestyle may be useful in the identification of individuals at higher risk of PD.

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Chapter 3 Tables

Table 3.1: Comparison of Case and Control Participants' Smoking, Alcohol and Early-Adult Personality Characteristics

	Cases (N=89)	**Controls (N=99)**	***P*-value (cases vs. controls)**
Smoking (% ever smoked)	49.44%	52.53%	0.67
Men	53.45%	63.64%	0.30
Women	41.94%	43.64%	0.88
Smoking pack-years (mean ± SD)	10.86 ± 18.47	12.43 ± 23.09	0.60
Men	12.23 ± 20.97	17.52 ± 29.00	0.31
Women	8.28 ± 12.41	8.36 ± 16.11	0.98
Alcohol (% ever drank)	85.39	81.82	0.51
Men	91.38	86.36	0.42
Women	74.19	78.18	0.68
Alcohol drink-years (mean ± SD)	61.35 ± 114.38	46.78 ± 80.83	0.32
Men	69.96 ± 119.69	77.95 ± 110.07	0.73
Women	45.25 ± 103.67	21.84 ± 28.01	0.23
Activity risks (young adult) (mean ± SD)	2.15 ± 1.91	2.45 ± 1.49	0.27
Men	2.79 ± 1.51	2.92 ± 1.62	0.68
Women	1.00 ± 2.04	2.08 ± 1.28	0.01
Routinization (young adult) (mean ± SD)	0.45 ± 1.39	0.18 ± 1.18	0.17
Men	0.18 ± 1.42	0.27 ± 1.20	0.73
Women	0.94 ± 1.20	0.10 ± 1.17	0.003

Table 3.2: Odds ratios and 95% confidence intervals for PD from multiple logistic regression models, adjusting for age, sex and education (age and education when stratified on sex).

Total Sample			
	Crude	**Adjusted for age, sex and education**	**Fully adjusted[a]**
Activity risks (age <35 years)	0.90 (0.76-1.08)	0.78 (0.63-0.97)[d]	0.74 (0.56-0.97) [d]
Routinization (age 20-35 years)	1.18 (0.93-1.50)	1.16 (0.90-1.50)	0.88 (0.63-1.24)
Smoking (ever)	0.88 (0.50-1.57)	0.67 (0.36-1.25)	-
Smoking (pack-years)[b]	0.96 (0.84-1.11)	0.90 (0.77-1.04)	0.92 (0.78-1.08)
Alcohol use (ever)	1.30 (0.60-2.83)	1.48 (0.63-3.49)	-
Alcohol consumption (drink-years) [c]	1.02 (0.99-1.05)	1.01 (0.98-1.04)	1.02 (0.99-1.06)
Men			
	Crude	**Adjusted for age and education**	**Fully adjusted[a]**
Activity risks (age 20-35 years)	0.94 (0.71-1.24)	0.88 (0.66-1.19)	0.77 (0.51-1.16)
Routinization (age 20-35 years)	0.95 (0.69-1.30)	0.94 (0.68-1.31)	0.71 (0.44-1.14)
Smoking (ever)	0.66 (0.29-1.46)	0.66 (0.29-1.50)	-
Smoking (pack-years)[b]	0.92 (0.78-1.08)	0.99 (0.94-1.05)	0.88 (0.74-1.06)
Alcohol use (ever)	1.67 (0.48-5.89)	2.24 (0.60-8.34)	-
Alcohol consumption (drink-years) [c]	0.99 (0.96-1.03)	1.00 (0.96-1.03)	1.02 (0.97-1.06)
Women			
	Crude	**Adjusted for age and education**	**Fully adjusted[a]**
Activity risks (age 20-35 years)	0.66 (0.49-0.90)	0.69 (0.50-0.95)[d]	0.73 (0.49-1.09)
Routinization (age 20-35 years)	1.83 (1.19-2.80)	1.63 (1.05-2.53)[d]	1.25 (0.73-2.15)
Smoking (ever)	0.93 (0.38-2.27)	0.62 (0.23-1.68)	-
Smoking (pack-years)[b]	1.00 (0.74-1.34)	0.90 (0.63-1.27)	0.96 (0.63-1.45)
Alcohol use (ever)	0.80 (0.29-2.24)	1.09 (0.36-3.37)	-
Alcohol consumption (drink-years) [c]	1.06 (0.97-1.16)	1.06 (0.97-1.16)	1.08 (0.96-1.22)

[a]Adjusted for age, sex and education as well as other personality indicators (except Ever Smoking and Ever Alcohol Use)
[b]units of 10 pack-years
[c]units of 10 drink-years
[d]$p<0.05$

Chapter 4

Occupational Characteristics and Patterns as Risk Factors for Parkinson's Disease

Abstract

Background: Associations have been reported between the risk of Parkinson's disease (PD) and employment in certain fields. Most occupational studies have focused on toxic exposures as potential causal explanations of these associations. However, PD also has been associated with personality characteristics including decreased risk-taking and novelty-seeking that may influence occupational choices and patterns.

Objective: To evaluate the role of personality as indicated by occupational choices and employment patterns in the risk of PD.

Methods: In-person interviews were conducted to assess occupational histories and early-adult personality indicators in 89 PD patients and 99 controls. Associations between occupational characteristics, personality and the risk of PD were examined.

Results: PD cases had fewer jobs in their lifetime than controls (mean for cases = 4.38 ± 2.20; mean for controls = 5.00 ± 2.26; p=0.03). There was no association between the number of categories of employment or the duration of the primary job and PD. Among women, PD was positively associated with more complex work with people (OR=0.69 (95% CI 0.53-0.89)), representing a 95% increased risk for PD comparing women whose jobs required the greatest complexity of work with people with those requiring the least complexity with people. Female cases also did less complex work with things compared with controls (OR=1.45 (95% CI 1.11-1.88)), translating into a 13-fold increased risk for

PD among women whose work involved the least complex work with things compared with the most. Occupational complexity was not associated with PD among men or across the sample regardless of sex. The number of jobs and number of job types was associated with taking more activity risks as a young-adult.

Conclusions: Cases with PD held fewer lifetime jobs compared with controls. Occupational complexity was associated with the risk for PD among women, but not men. Further consideration of the possible influence of personality on occupational choices is warranted.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that has been associated with employment in certain occupations. Health care workers, farmers, teachers, lawyers and scientists have been found to be at increased risk for PD [1-16], and individuals employed in the fields of construction, management and service have a reduced risk [11, 13, 17]. Most occupational studies have focused on toxic exposures such as welding [18-20], pesticide exposure [4, 5, 15, 21-24], exposure to magnetic fields [25] and exposure to infectious substances [11] as potential mechanisms associated with the risk for PD.

It has been suggested that PD is associated with a rigid, cautious and introverted personality type [26]. Previous epidemiologic studies report that PD cases are more cautious, introverted, compulsive, industrious, morally rigid, punctual, serious, stoic, and quiet and have reduced novelty- and sensation-seeking compared with controls [27-29]. We have found that increased risk-taking as a young adult is associated with a reduced risk for PD (OR=0.78 (95% CI 0.63-0.97)) and higher levels of routinization as a young adult are associated with an increased risk of PD among women (OR=1.63 (95% CI 1.05-2.53)) [30]. PD also has been associated with reduced novelty-seeking [29, 31].

Jobs involving greater complexity working with people have been associated with a reduced risk of Alzheimer's disease [32]. However, occupational complexity has only been studied as a risk factor for PD in one other study [33]. Choice of main lifetime occupations with distinctive complexity characteristics could be influenced by personality dimensions. For example, given the Parkinsonian personality traits of

introversion and compulsiveness [27-29], individuals with PD might be more likely to be employed in fields requiring a high level of data involvement such as accounting or engineering rather than those requiring interaction with people such as service or sales.

Given the description of the Parkinsonian premorbid personality as being rigid and cautious [26], we hypothesized that individuals with PD might be less likely to change jobs frequently or to alter the type of work they do during adulthood. The number and variety of jobs has not been studied with regard to the risk for PD. The aim of the present study was to assess the role of occupational characteristics and employment patterns as risk factors for PD and to examine the association of characteristics of occupations with aspects of personality that have been shown to be associated with PD.

Methods

Subjects

Subjects were identified through review of electronic medical records at an academic-based medical center. Charts of patients who visited the Movement Disorders clinic at the University of South Florida (USF) between January 1, 2007 and May 1, 2010 were reviewed to identify potential cases. A computer-generated list of patients who visited the USF Family Medicine clinic was used to identify potential controls. All potential cases and a random sample of potential controls were contacted first by mail, then by telephone to recruit and screen them for the study. All subjects were aged 50-80 years, Caucasian, free from memory impairment and able to read and speak English. Cases were further screened and deemed ineligible if they had a diagnosis of atypical PD, a history of

neurosurgery for PD, or severe motor fluctuations (greater than 50% of the day "off" or with dyskinesia). In order to increase the sample size, additional cases were recruited from two outlying neurology clinics. All subjects provided written informed consent prior to completing the study questionnaires according to the protocol approved by the Institutional Review Board.

Procedures

Trained interviewers completed private, in-person assessment of subjects at the study site (medical clinic) using highly structured questionnaires.

Exposures

Employment history

Each subject was asked to recall every paid job held for at least one year throughout their life. Job title, industry, job duties and the year the job began and ended were recorded. For jobs in which subjects were currently or recently employed, we used a reference year approach for cases and controls. Each case was assigned his/her own reference year based on age at symptom onset – 1 year. For example, a 65 year old case whose symptoms began at age 60 was assigned a reference year corresponding to the year in which they were 59 years old. We then stratified age by 10-year intervals and calculated the mean reference age for cases within each stratum. Controls were assigned a reference age equal to the mean reference age of cases in each age stratum. These reference ages were used when calculating the number of jobs and number of job categories (described below).

Occupation variables

Occupational variables were defined based on subjects' employment histories and DOT codes corresponding to each job they reported. All occupational data were coded blinded to case-control status. Employment data were coded according to the Dictionary of Occupational Titles (DOT) [34] job classification system by the same coder (KLS). The DOT provides unique 9-digit codes for occupations based on job title, industry and duties (Table 4.1).

The first digit of each occupational code identifies the occupation as belonging to 1 of 9 categories (see Table 4.1). The second and third digits of the DOT code provide additional distinctions within each occupational category. For example, the prefix of the DOT code for a kindergarten teacher is 092 while the code for a driver education teacher is 099. Both the kindergarten teacher and driver education teacher are in the same general category as indicated by the common first digit (0=professional, technical and managerial) and second digit (09=occupations in education), but their jobs differ within this category as indicated by the third and subsequent digits (092=occupations in preschool, primary school and kindergarten education; 099= occupations in education not elsewhere classified).

The middle 3 digits of the DOT code define the complexity of the occupation with regard to people, data and things with lower codes (closer to 0) for each component indicating more complex work in that area (Table 4.1). For example, "operating"

equipment (code 2) requires more complex work with “things” than “tending” equipment (code 5). It is important to note that lower DOT codes indicate more complex work.

Number of jobs

The number of jobs reported by each subject up until the reference age was summed. Each job counted individually, even if it had the same title as a previously reported job. For example, a subject who reported employment as a kindergarten teacher 3 separate times or at 3 schools was considered to have worked in 3 jobs.

Number of job categories

We used changes in the first 3 digits of subjects’ DOT codes to indicate changes in job categories with each unique 3-digit code for this field indicating a unique category of job for that subject. The number of job categories in which a subject worked prior to their reference age was summed. For example, a subject who was initially employed as a kindergarten teacher (DOT code beginning with 092), later employed as a special education teacher (DOT code beginning with 094), and finally employed as a university professor (DOT code beginning with 090) was considered to have been employed in 3 job categories. A subject who reported initial employment as a kindergarten teacher (DOT code beginning with 092), later employment as a special education teacher (DOT code beginning with 094), and final employment as a kindergarten teacher (DOT code beginning with 092) was considered to have been employed in 2 job categories since the first and last job have the same DOT category (092).

Duration of employment

Duration of employment at each job was calculated by subtracting the year a job started from the year the job ended, taking reference ages into account. For example, employment after the age of 59 years was not included for a participant with a reference age of 59 years, even if the participant was currently employed.

Duration of longest-held job

The duration of employment at the job with the longest duration was recorded as the duration of the longest-held job, taking reference ages into account, as with duration of employment, above.

Primary lifetime occupation

The job with the longest duration was considered each subject's primary lifetime occupation.

Covariates

Personality

Personality characteristics related to risk-taking and preference for a routine lifestyle were indirectly assessed through the use of instruments that used subjects' participation in routine and risk-taking activities as a young adult [30, 35], such as preferences for doing the same activities each day, gambling for small and large sums of money, swimming far from shore, riding a motorcycle or roller coaster, parachuting out of an airplane, parasailing, skiing and flying in a small plane. Latent variable values

representing early-adult activity risks and early-adult routinization were calculated using results from factor analyses [35].

Other Covariates

The study interview also included subjects' current age, sex, and number of years of formal education.

Data Analysis

The crude association of demographic and occupational variables with case-control status was examined using Wilcoxon Rank-Sum tests for continuous variables and chi-square tests for discrete variables. The association of occupational characteristics with the risk of PD was analyzed using multiple logistic regression, controlling for age, sex and education.

We also examined Pearson correlations between occupational variables and early-adult measures of risk-taking and routinization, partialling out the effects of age, sex and education. Additionally, sex was examined as a potential effect-modifier of these associations.

P-values of less than 0.05 (2-sided test) were interpreted as being statistically significant. All data were analyzed using SAS version 9.2 [36].

Results

Eighty-nine cases (56% of 125 who were eligible at the main study site plus 19 from outlying sites) and 99 controls (48% of 207 who were eligible) completed study assessments. Full participation data including reasons for refusal have been detailed previously [35]. Cases and controls did not differ by mean age (Table 4.2). However, cases were more likely to be men (p=0.005) and to have fewer years of formal education compared with controls (p=0.003). Educational differences were particularly pronounced among women.

Occupational patterns

All subjects reported employment in at least 1 job. Cases held an average of 4.38±2.20 jobs compared with 5.00±2.26 jobs for controls (p=0.03) and worked in an average of 3.40±1.74 types of jobs compared with 3.63±1.92 types of jobs among controls (p=0.47). Among men, there were no significant differences between cases and controls in the mean number of jobs, number of job categories, or duration of primary occupation, while women with PD worked in fewer jobs (mean= 3.81±1.70) compared with women without PD (mean=4.85±2.43) (p=0.04) (Table 4.2).

Occupational categories

In our data, cases' and controls' primary occupation was most often in the category of "professional, technical and managerial" (cases 60%, controls 63%). This occupational category is quite broad and comprises occupations in architecture, engineering, surveying, mathematics, sciences, medicine and health, education, law, religion, art,

entertainment, administration (accounting, human resources, purchasing) and management. Within this category, the most common field for lifetime occupation of both cases and controls was education (DOT codes beginning with "09"), with 11.24% of cases and 11.11% of controls reporting main occupations in this category. There was no association between the first DOT digit and case-control status.

Occupational complexity

None of the occupational complexity characteristics showed a statistically significant difference between cases and controls in the total sample.

Occupation and Risk of PD

In logistic regression models adjusted for age, sex, and education, PD was associated with the number of jobs held (OR=0.87 (95% CI 0.75-1.00) p=0.048), but not with the number of job categories (OR=0.88 (95% CI 0.74-1.05)) or the duration of the longest held job (OR=1.00 (95% CI 0.97-1.04)) in the total sample (Table 4.3). PD was also not associated with complexity of work with data (OR=0.99 (95%CI 0.80-1.23)) or things (OR=1.02 (95% CI 0.90-1.16)). However, a borderline significant association was seen between higher complexity of work with people and greater risk of PD (OR=0.87 (95% CI 0.75-1.00), p=0.053. Among women, PD was associated with greater complexity of work with people (OR=0.69 (95% CI 0.53-0.89)) and less complex work with things (OR=1.45 (95% CI 1.11-1.88)).

Occupation and Personality

Taking more activity risks in early adulthood was positively associated with the number of jobs (r=0.19, p=0.02) and with the number of types of jobs (r=0.26, p=0.001), partialling out the effects of age, sex and education (Table 4.4). Routinization was not associated with either the number of jobs or the number of types of jobs. Complexity of work with people, data and things was not associated with early-adult activity risks or routinization.

Discussion

In this case-control study, we found an association among women between higher risk of PD and greater complexity of work with people as well as less complexity of work with things. Women whose jobs required the greatest possible complexity of work with people were approximately 95% more likely to have PD compared with those whose work required the least possible complexity of work with people. In addition, women with the least complex work with things were over thirteen times more likely to have PD compared with women with the most complex work with things. There was a marginally significant association between risk of PD and higher complexity of work with people in the entire sample as well as an association between PD and the number of jobs held over the lifetime.

While the association of PD and greater complexity of work with people might seem to contradict previous descriptions of the Parkinsonian personality as introverted [27], the DOT coding for this characteristic does not reflect the *frequency* of work with people.

Individuals who are unlikely to take risks and who enjoy predictable routines would seem to be best suited for jobs involving supervision, instruction and mentoring, which all have DOT codes representing the greatest amounts of complexity of work with people (Table 4.1). Jobs with less complexity of work with people such as serving and helping are jobs that might offer less dependability and require greater risks, thereby having less appeal to people with personality characteristics such as those present in PD.

Effect-modification by sex was evident with associations between PD and complexity of work with people and things present among women but not men. Given the prevailing societal expectations and gender roles that were more strongly held in past decades, it is likely that women had fewer occupational choices that were easily obtainable. It is possible that women who had more assertive or determined personalities would have been more likely to work in a broader range of occupations compared with women who were content with more traditional occupational choices. Therefore, personality might have differentially influenced occupational choices more in women than in men.

A recent study [33] examined personality aspects of occupation as risk factors for PD by evaluating the demands, skills and aptitudes required by the participants' longest held job using US Census Occupational Codes [33]. Occupations that required more adaptability, ability to make generalizations or preference for abstract activities were marginally inversely associated with the risk of PD (OR for adaptability =0.84 (95% CI 0.70-1.02); OR for ability to make generalizations = 0.85 (95% CI 0.72-1.00); OR for abstract activities = 0.90 (95% CI 0.76-1.06)). Since employment history following the onset of

PD symptoms was not censored, it is possible that these findings are biased by the presence of symptomatic PD; however, the duration of the longest-held job was over 30 years for both cases and controls, which reduces the likelihood that this occurred. Although the DOT coding system we used does not provide insight into these aspects of occupation, the finding of decreased flexibility among cases with PD is consistent with our previous report of an inverse association between PD and a preference for routine during early-adulthood [35].

Other previous studies of occupational risk factors for PD have yielded inconsistent results. An increased risk for PD was found among individuals with a history of employment in health care (including medicine and dentistry) [7-11, 13, 37], farming and agricultural work [1-6, 9, 10, 13-16], teaching [7-11], science [9], religion [9], legal work [9, 11], hunting [13], and forestry [13]. Other case-control studies reported a reduced risk for PD among those employed in manufacturing [13], transportation [13], management [11], clerical fields [11], construction [11] and service professions[13, 17]. Conversely, several studies have failed to find any association between PD and farming [23, 24, 38-44] including a case-control study of 404 incident cases of PD [42]. A smaller Italian study failed to find any association between PD and occupations [38].

Other studies have used DOT codes to evaluate the association of occupation with PD. A nested case-control study evaluated occupational histories of 144 cases with PD and 464 control subjects [17]. Subjects who reported ever working in the “service” category had a lower risk for PD (OR=0.56, p=0.01 adjusted for age, sex and race). There were no

associations with other DOT categories. Another population-based case-control study examined occupations and the risk for PD in 404 incident cases and 526 controls in Washington state [42]. There was no association between PD and any DOT category among men or women, adjusting for age, ethnicity and smoking. Finally, the largest study that used DOT coding in examining risk factors for PD was a multi-center case-control study conducted in Scotland, Sweden, Italy and Romania [45] that evaluated 649 cases with PD and 1,587 controls. A history of ever working in "processing occupations" was associated with a reduced risk of PD ((OR=0.69 (95% CI 0.50-0.95) adjusting for age, sex, ever-use of tobacco and family history of PD). Similarly, there was no association between risk for PD and a primary occupation in any DOT category in our study, either crudely (p=0.38) or adjusted for age, sex and history of ever smoking (p=0.85). This difference could be due to the high educational level obtained by controls relative to cases or to the urban setting of the center from which subjects were recruited. Also, few subjects reported working in certain occupational categories, which limited the statistical power to obtain significant findings if they existed.

A strength of our study is that all assessments were conducted via in-person interviews which helped ensure completeness of data collection and reduce the frequency of invalid responses and missing data. The personality assessments used in this study were unique in that they used activities and events as historical indicators of personality traits and full occupational histories. While environmental influences have been shown to affect the risk of PD, latent personality changes associated with the disease process could influence

occupational decisions. Our findings that higher complexity of work with people is associated with increased PD risk among women warrants further study.

Several limitations were present in this study due to sample selection. Since our study was based in an urban academic medical center, referral bias may be present and personality characteristics could result in certain individuals requesting referrals to our center. There was also a high percentage of educators in our sample and it is possible that individuals with teaching backgrounds were more likely to be patients at an academic medical clinic or to participate in research studies. Such restriction may have resulted in increased homogeneity of the sample that would drive the measures of association toward the null. Another limitation is the possibility of imprecision in DOT coding. Although the DOT categories provide a structured system for classifying and grouping similar occupations, this aggregation may obscure associations between specific occupations and PD. Such misclassification would have occurred independently of case-control status, biasing the OR toward the null. We considered only the subjects' primary occupation for all analyses rather than their complete job histories. It is possible that exposures occurred during employment of shorter duration and were not captured by this analysis. Additionally, since our aims included several exploratory analyses, we did not adjust for multiple comparisons, and results should be interpreted with this in mind. Finally, it is possible that the primary lifetime occupation may have been influenced by very early disease symptoms. However, given the eligibility criteria requiring cases to have been diagnosed with PD no more than 10 years prior to study entry, it is expected that their

choice of primary occupation occurred well before the onset of PD symptoms (as indicated by duration of primary occupation of approximately 20 years).

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Chapter 4 Tables

Table 4.1: Components of the DOT code

DOT Code: A # # X Y Z # # #							
"A" component (Category)		**"X" component (Data complexity)**		**"Y" component (People complexity)**		**"Z" component (Things complexity)**	
Value	**Meaning**	**Value**	**Meaning**	**Value**	**Meaning**	**Value**	**Meaning**
0/1	Professional, technical, and managerial	0	Synthesizing	0	Mentoring	0	Setting up
2	Clerical and sales	1	Coordinating	1	Negotiating	1	Precision working
3	Service	2	Analyzing	2	Instructing	2	Operating/ controlling
4	Agricultural, fishery and forestry	3	Compiling	3	Supervising	3	Driving/ operating
5	Processing	4	Computing	4	Diverting	4	Manipulating
6	Machine trades	5	Copying	5	Persuading	5	Tending
7	Benchwork	6	Comparing	6	Speaking	6	Feeding/ offbearing
8	Structural work			7	Serving	7	Handling
9	Miscellaneous			8	Taking instructions/ helping		

Adapted from [33]

Table 4.2: Demographic characteristics

		Cases			Controls		
		Total (N=89)	**Men (N=58)**	**Women (N=31)**	**Total (N=99)**	**Men (N=44)**	**Women (N=55)**
Age, in years [a]		68.47 ± 8.00 (50 – 80)	68.74 ± 8.10 (50-80)	67.97 ± 7.91 (51-79)	67.31 ± 6.96 (50 – 80)	69.05 ± 6.44 (55-80)	65.93 ± 7.11 (50-79
Sex (% men)		65.17% [c]			44.44% [c]		
Education – highest grade completed [a]		14.81 ± 3.10 (8 – 24) [c]	15.21 ± 3.07 (8-24)	14.06 ± 3.08 (9-23) [c]	16.26 ± 3.54 (9 – 24) [c]	16.20 ± 3.41 (11-24)	16.31 ± 3.67 (9-24) [c]
Number of jobs [a]		4.38 ± 2.20 (1-13) [c]	4.69 ± 2.38 (1-13)	3.81 ± 1.70 (2-8) [c]	5.00 ± 2.26 (1-12) [c]	5.19 ± 2.04 (1-9)	4.85 ± 2.43 (1-12) [c]
Number of job categories [a]		3.40 ± 1.74 (1-10)	3.66 ± 1.90 (1-10)	2.94 ± 1.29 (1-6)	3.63 ± 1.92 (1-11)	3.82 ± 1.60 (1-7)	3.47 ± 2.14 (1-11)
Duration of longest-held job (years) [a]		21.10 ± 10.75 (3-46)	24.07 ± 10.20 (6-46)	15.55 ± 9.62 (3-37)	19.58 ± 10.56 (2-45)	21.95 ± 10.75 (2-41)	17.67 ± 10.10 (2-45)
Category of occupation (% of subjects) [b]	0/1: Professional, technical, and managerial	60	55	68	63	59	65
	2: Clerical and sales	15	12	19	18	14	22
	3: Service	8	10	3	6	7	5
	4: Agricultural, fishery and forestry	2	2	3	3	0	5
	5: Processing	3	5	0	0	0	0
	6: Machine trades	4	5	3	3	7	0
	7: Benchwork	1	0	3	1	0	2
	8: Structural work	4	7	0	5	11	0
	9: Miscellaneous Occupations	2	3	0	1	2	0
Complexity of work with people [a,b]		4.69±2.50 (0-8)	4.98±2.35 (0-8)	4.13±2.70 (0-8)	4.66±2.47 (0-8)	4.68±2.51 (0-8)	4.65±2.46 (0-8)
Complexity of work with data [a,b]		2.03±1.63 (0-6)	1.81±1.52 (0-6)	2.45±1.79 (1-6)	1.96±1.34 (0-6)	1.70±1.13 (0-6)	2.16±1.46 (0-6)
Complexity of work with things [a,b]		5.02±2.54 (0-7)	4.53±2.68 (0-7)	5.94±2.00 (1-7)	5.19±2.45 (1-7)	5.50±2.48 (1-7)	4.94±2.41 (1-7)

[a] mean ± sd (range)
[b] primary lifetime occupation
[c] $p<0.05$ cases compared with controls (crude)

Table 4.3: Association of occupational characteristics with PD (OR (95%CI))

	Total Sample (n=188)[a]	**Men (n=102)[b]**	**Women (n=86)[b]**
Number of jobs	0.87 (0.75-0.999) [d]	0.90 (0.75-1.08)	0.82 (0.64-1.05)
Number of job categories	0.88 (0.74-1.05)	0.92 (0.73-1.16)	0.84 (0.63-1.13)
Duration of longest-held job	1.00 (0.97-1.04)	1.03 (0.99-1.07)	0.98 (0.93-1.03)
Complexity of work with data[c]	0.99 (0.80-1.23)	1.00 (0.73-1.36)	0.94 (0.69-1.29)
Complexity of work with people[c]	0.87 (0.75-1.002)	0.98 (0.81-1.19)	0.69 (0.53-0.89) [d]
Complexity of work with things[c]	1.02 (0.90-1.16)	0.88 (0.75-1.03)	1.45 (1.11-1.88) [d]

[a]Adjusted for age, sex and education
[b]Adjusted for age and education
[c] Lower code indicates greater complexity
[d]$p<0.05$

Table 4.4: Partial correlation coefficients of occupational characteristics and young-adult personality indicators (adjusted for age, sex and education)

	Activity risks (young adult)	**Routinization (young adult)**
# jobs	0.19[c]	-0.13
# job types	0.26[c]	-0.15
Work with people[a,b]	-0.02	-0.07
Work with data[a,b]	--0.04	0.001
Work with things[a,b]	-0.05	0.03

[a]Based on primary occupation
[b] Lower code indicates greater complexity
[c]$p<0.05$

Chapter 5

Conclusions and Recommendations

This study resulted in a number of important findings. These are summarized here and recommendations are made for future research.

Conclusions

PD was associated with higher current levels of neuroticism and harm-avoidance. In cases and controls separately, early-life indicators and late-life measures of dopamine-related personality characteristics including novelty-seeking and harm-avoidance were significantly and consistently correlated. This suggests that personality traits are likely stable not only in individuals with normal dopaminergic function, but also in cases with dopaminergic dysfunction.

Taking “activity risks” such as riding on roller coasters as a young adult and higher levels of current harm-avoidance were found to reduce the odds of PD in this study. Current levels of novelty-seeking were associated with a reduced odds of disease among men while early- adult routinization increased the odds of disease among women. Taking or wanting to take “activity risks” such as riding on roller coasters as a young adult, a characteristic related to dopaminergic function, was found to reduce the odds of PD in

this study and suggests that people with PD may have had lower dopaminergic function relatively early in life.

Parkinson's disease was inversely associated with employment in fewer jobs (OR=0.87 (95% CI 0.75-0.99)). Among women, complex work with people was associated with a reduced risk for PD (OR=0.69 (95% CI 0.53-0.89)) while complex work with things was associated with increased risk (OR=1.45 (95% CI 1.11-1.88)). Other aspects of occupational histories were not statistically significant including the number of types of jobs or the duration of the primary occupation.

In this study, smoking was not found to be statistically associated with PD, although the Odds Ratio for ever smoking was entirely consistent with that observed in most case-control studies (OR=0.67 (95% CI 0.36-1.25)). However, alcohol consumption was not associated with the risk for PD (OR=1.01 (0.98-1.04)) as has been reported in other studies. The controls in this study were highly educated and may have engaged in healthier behaviors, such as lower alcohol consumption, than the general population; therefore the p_o (proportion of exposed controls) among controls may be under-estimated vis-à-vis the population from which the cases came, potentially obscuring our ability to statistically detect an inverse OR if one exists. The association between PD and caffeine consumption could not be examined because the questionnaire used to assess caffeine intake recorded the lifetime consumption of coffee and tea but did not capture changes between caffeinated and decaffeinated beverages. Therefore, if an individual currently

drank decaffeinated coffee, for example, but drank caffeinated coffee for the previous 49 years, they would appear to have consumed 50 years of decaffeinated coffee.

Description of PD Cases

Characteristics of PD in the study sample are shown in Table 5.1. Although the study inclusion criteria required cases to have been diagnosed with PD for no more than 10 years, a wide range of years of disease duration is evident in the self-reported age of disease onset and duration. Almost all cases were taking medication for PD, with over 80% currently taking levodopa.

Table 5.1 Description of PD Cases

		Total (n=89)	Men (n=58)	Women (n=31)
Age of PD onset*		60.03 ± 11.89 (21-79)	59.79 ± 12.74 (21-79)	60.48 ± 10.31 (37-78)
Years since PD onset*		8.43 ± 7.39 (0-40)	8.95 ± 8.17 (0-40)	7.48 ± 5.64 (1-24)
Medication for PD (%)		93	97	87
Years since first PD medication started*		5.38 ± 3.63 (0-15)	5.48 ± 3.77 (0-15)	5.15 ± 3.39 (1-15)
Levodopa for PD (%)		84	86	81
Years since levodopa started*		4.49 ± 3.58 (0-14)	4.47 ± 3.78 (0-14)	4.55 ± 3.15 (0-11)
Stage (Hoehn & Yahr)*		2.14 ± 0.46 (1-4)	2.22 ± 0.77 (1-4)	1.98 ± 0.75 (1-4)
UPDRS total score*		34.60 ± 17.85 (3-73)	37.93 ± 17.99 (8-73)	28.35 ± 16.05 (3-62)
Side of worst impairment (%)	Right	45	40	55
	Left	36	40	29
	Unknown	19	21	16

* mean ± SD (range)

In addition to the associations examined as part of the specific aims, bivariate correlations between all of the demographic and exposure variables are shown in Tables A.2-A.5 in Appendix 2 (with associations among cases shown in Tables A.6-A.9 and among controls in Tables A.10-A.13). These correlations show the relation of the various personality measures and indicators and the similarities between the associations in cases and controls.

Consistency and Implications of Findings

The demographic characteristics of the study sample were consistent with previous PD research with regard to sex [6, 9]. Although an increased risk for PD with advancing age is well established [6-8], age was not associated with PD in this study (mean age among cases = 68.47 ± 8.00 years, mean age among controls = 67.31 ± 6.96 years, p=0.29) which may reflect the restriction of the study to people aged 50-80 years.

The results of this study build on previous findings of the role of personality characteristics in PD. Several case-control studies have found that PD patients have reduced leadership tendencies, flexibility and sociability and are more quiet, generous, cautious, and even-tempered during the time period prior to the onset of PD compared with controls [40-42]. Retrospective assessment of personality also has shown that PD patients have high premorbid levels of introversion and obsessive-compulsive tendencies [43]. Case-control studies have found reduced sensation- seeking [45], higher novelty-seeking [36, 46] and higher harm-avoidance [46, 47] in cases with PD compared with

normal [45, 46] and medical [36, 47] controls. Longitudinal and cross-sectional data indicate a high degree of stability in personality traits during adulthood [28-30].

Similarly, we found a stable association among many traits, particularly traits that are driven by dopaminergic function. This stability was present not only among controls with presumably normal dopaminergic function throughout their lives, but also among cases. Our finding of correlations between personality factors in these time periods in both cases and controls (separately) validates the association of these early-adult personality traits and PD and supports the hypothesis that behaviors associated with PD personality exist many years and even decades before the presentation of motor symptoms. The observed temporal stability of traits such as novelty- seeking, harm-avoidance and risk-taking in this study suggests the possibility of dopaminergic deficiency in people destined to develop PD and the possibility of a lengthy presymptomatic period, perhaps life-long, of the disease. These results advance current knowledge about the etiology of PD and provide insights into the duration of the presymptomatic phase of the disease.

In our study, the estimated risk for PD was not associated with main lifetime occupation in the fields of agriculture, education or medicine as has been reported in previous studies [16, 46, 49, 50]. This difference could be due to the higher educational level obtained by controls relative to cases or to the urban setting of the center from which subjects were recruited. Seven controls and 0 cases reported a main lifetime occupation beginning with code 090 which corresponds to “occupations in college and university education”. Of

these 7, 1 was an academic dean and 6 had codes corresponding to “faculty member, college or university”.

Strengths and Limitations

The assessments used in this study were unique in that they used objective activities and behaviors as retrospective indicators of personality traits. Previous studies of premorbid personality have employed subjective assessments that are more likely to be affected by recall bias. For example, subjects are likely to be able to recall events such as riding on roller coasters or swimming far from shore in different time periods in their lives accurately. These are considered more objective measures of personality preferences. Posing questions about “taking risks” is a subjective means of ascertaining such exposures and the answers would depend not only on recall and social desirability of the responses, but also on personal interpretation of what “taking risks” constitutes. Although a retrospective design always poses the potential for recall bias, the use of objective measures reduces the probable magnitude of such bias. Like cases, controls were selected from a medical clinic. The potential for selection bias related to factors associated with the probability of seeking medical care (such as socioeconomic status and education) and of being diagnosed with PD if symptoms are present is minimized by recruiting cases and controls from the same study base.

Given the eligibility criteria requiring cases to have been diagnosed with PD no more than 10 years prior to study entry, it is expected that their choice of primary occupation occurred well before the onset of PD symptoms and was not influenced by physical

symptoms of the disease. Cases started working in their primary occupation at a mean age of 31.97±10.15 years (similar to a mean age of 31.85±9.57 years for controls), which was an average of approximately 30 years before the onset of PD symptoms (Table 5.1). This study is unique in that it is one of the first to evaluate personality aspects of occupation as risk factors for PD. Although occupational environmental influences may affect the risk for PD, latent personality changes associated with the disease process could influence occupational selection.

We did not assess depression in our study and its relation to PD and the potential influence of depression as a mediating variable or as a confounder could not be evaluated. In healthy individuals [56] and subjects suffering from major depression [57], harm-avoidance has been reported to be associated with serotonin levels. High levels of harm-avoidance have been shown to be associated with high serotonergic release from presynaptic neurons and down-regulation of postsynaptic serotonergic receptors [58]. Other studies have reported dopaminergic activity as the primary influence of this trait [35]. Kaasinen et al. [47] reported that harm-avoidance was correlated with ^{18}F-dopa uptake in the right caudate nucleus in these subjects (r=0.53, p=0.04). Interestingly, differences in novelty-seeking and harm-avoidance in individuals with PD compared with controls have been reported to depend on the brain hemisphere where dopamine loss was most pronounced [59]. Forty PD patients were compared with 17 age-matched controls and reduced novelty-seeking was found among cases with greater dopamine loss in the left hemisphere [59]. Cases with lower dopamine levels in the right hemisphere reported

higher levels of harm-avoidance. The relation of clinical features of PD in our sample and personality measures will be examined in future analyses.

Statistical power for this study was calculated in the design phase. It was determined that in order to achieve 80% power for our primary aims, 200 cases and 400 controls were needed detect an OR of 1.70 if $p_o = 0.40$. Enrolling a sufficient number of cases and controls was challenging and post-hoc calculated power based on results from the occupational portion of the study was only 48%. Therefore, some differences might not have been detected due to the small sample size. Although most aspects of occupational choices were not associated with the odds of PD in our study, dopaminergic aspects of personality were related to occupational choices and future consideration of this hypothesis is warranted.

Future Research

Several additional analyses are possible with the study data. Since there is no published validated measure of routinization, an instrument was developed (by KLS) to measure routinization for this study. Additional research to validate this instrument would be beneficial. Also, the association between disease severity and duration, types of symptoms, and medication use with personality characteristics among the cases could provide insight into the effects of the disease and treatment on personality. Additionally, the relation of depression to the association between premorbid personality and PD would be of interest in future studies.

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Appendix 1: Bivariate Correlations

Table A.2: Bivariate correlations of early-adult personality traits among all subjects

Variable	Activity Risks (age <35 years)	Lifestyle Risks (age <35 years)	Routinization (age 20-35 years)
PD	-0.09	0.02	0.11
Age (Years)	-0.13	0.07	0.17*
Sex	-0.34**	-0.29**	0.07
Education – highest grade completed	0.04	-0.07	-0.16*
Neuroticism[a]	-0.21**	-0.10	0.21**
Extraversion[a]	0.29**	-0.05	-0.34**
Openness[a]	0.12	-0.03	-0.28**
Agreeableness[a]	-0.21**	-0.19*	0.02
Conscientiousness[a]	0.10	0.06	0.004
Novelty-seeking[b]	0.28**	0.04	-0.35**
Harm-avoidance[b]	-0.38**	-0.11	0.36**
Reward dependence[b]	-0.14	-0.22**	0.04
Persistence[b]	0.02	-0.04	-0.0001
Self-directiveness[b]	0.17*	0.10	-0.07
Cooperativeness[b]	-0.07	-0.07	-0.05
Self-transcendence[b]	0.04	-0.15	-0.08
Number of jobs	0.21**	0.07	-0.19**
Number of job categories	0.29**	0.20**	-0.20**
Complexity of work with people[c]	-0.01	0.09	0.01
Complexity of work with data[c]	-0.10	-0.002	0.06
Complexity of work with things[c]	-0.06	-0.05	-0.01
Smoking (ever)	0.20*	0.48**	-0.13
Smoking (pack-years)	0.24**	0.70**	-0.20**
Alcohol use (ever)	0.24**	0.24**	-0.19*
Alcohol consumption (drink-years)	0.17*	0.71**	0.13
Activity Risks (age <35 years)	1.00	0.33**	-0.60**
Lifestyle Risks (age <35 years)	-	1.00	-0.05
Routinization (age 20-35 years)	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.3: Bivariate correlations of current personality traits among all subjects

Variable	Neuroticism[a]	Extraversion[a]	Openness[a]	Agreeableness[a]	Conscientiousness[a]	Novelty-seeking[b]	Harm-avoidance[b]	Reward dependence[b]	Persistence[b]	Self-directiveness[b]	Cooperativeness[b]	Self-transcendence[b]
PD	0.15*	-0.04	-0.18*	-0.03	-0.12	0.12	0.12	-0.08	0.05	-0.16*	-0.18*	-0.06
Age (Years)	-0.22**	-0.05	-0.26**	0.02	-0.06	-0.21**	-0.15*	0.11	-0.32**	0.0004	-0.09	-0.09
Sex	0.10	0.04	0.11	0.33**	0.08	-0.02	0.13	0.27**	0.02	-0.02	0.27**	0.02
Education – highest grade completed	-0.10	0.15*	0.51**	0.08	-0.03	0.07	-0.01	-0.07	-0.01	0.16*	0.06	-0.06
Activity Risks (age <35 years)	-0.21**	0.29**	0.12	-0.21**	0.10	0.28**	-0.38**	-0.14	0.02	0.17*	-0.07	0.04
Lifestyle Risks (age <35 years)	-0.10	-0.05	-0.03	-0.19*	0.06	0.04	-0.11	-0.22**	-0.04	0.10	-0.07	-0.15
Routinization (age 20-35 years)	0.21**	-0.34**	-0.28**	0.02	0.004	-0.35**	0.36**	0.04	-0.0001	-0.07	-0.05	-0.08
Number of jobs	0.02	0.17*	0.15*	-0.04	0.03	0.05	-0.10	-0.09	0.07	0.13	0.04	0.13
Number of job categories	-0.04	0.13	0.10	-0.13	0.003	0.16*	-0.17*	-0.14	0.11	0.13	0.002	0.09
Complexity of work with people[c]	0.002	-0.07	-0.19**	-0.05	-0.01	-0.07	-0.09	0.02	-0.01	-0.10	-0.03	0.18*
Complexity of work with data[c]	-0.003	-0.22**	-0.02	-0.02	-0.09	0.09	0.01	-0.004	-0.02	-0.05	-0.04	0.04
Complexity of work with things[c]	0.04	-0.02	0.06	0.03	0.02	0.04	0.02	-0.04	0.10	0.03	-0.04	-0.02
Smoking (ever)	-0.10	-0.17*	-0.02	-0.10	-0.06	0.04	0.01	-0.14	-0.10	0.12	0.03	-0.07
Smoking (pack-years)	-0.07	-0.08	0.06	-0.16*	0.07	0.07	-0.07	-0.22**	-0.04	0.06	0.02	-0.06
Alcohol use (ever)	-0.12	-0.004	0.12	-0.11	-0.02	0.10	-0.05	-0.10	-0.10	-0.005	-0.13	-0.10
Alcohol consumption (drink-years)	-0.06	-0.02	-0.07	-0.16*	0.03	0.05	-0.06	-0.17*	-0.08	-0.01	-0.13	-0.21**
Neuroticism[a]	1.00	-0.42**	0.02	-0.21**	-0.41**	0.04	0.70**	0.02	-0.03	-0.56**	-0.23**	0.12
Extraversion[a]	-	1.00	0.14	0.25**	0.39**	0.25**	-0.62**	0.26**	0.32**	0.21**	0.18*	0.25**
Openness[a]	-	-	1.00	0.08	-0.02	0.30**	-0.07	-0.005	0.17*	0.05	0.18*	0.25**
Agreeableness[a]	-	-	-	1.00	0.37**	-0.19*	-0.10	0.43**	-0.02	0.22**	0.57**	0.06
Conscientiousness[a]	-	-	-	-	1.00	-0.22**	-0.38**	0.14	0.40**	0.45**	0.36**	0.06

Table A.3 (Cont)

Variable	Neuroticism[a]	Extraversion[a]	Openness[a]	Agreeableness[a]	Conscientiousness[a]	Novelty-seeking[b]	Harm-avoidance[b]	Reward dependence[b]	Persistence[b]	Self-directiveness[b]	Cooperativeness[b]	Self-transcendence[b]
Novelty-seeking[b]	-	-	-	-	-	1.00	-0.17*	-0.13	-0.02	-0.22**	-0.17*	0.20**
Harm-avoidance[b]	-	-	-	-	-	-	1.00	-0.08	-0.15*	-0.48**	-0.22**	-0.16*
Reward dependence[b]	-	-	-	-	-	-	-	1.00	0.04	0.07	0.45**	0.17*
Persistence[b]	-	-	-	-	-	-	-	-	1.00	0.08	0.05	0.32**
Self-directiveness[b]	-	-	-	-	-	-	-	-	-	1.00	0.38**	-0.12
Cooperativeness[b]	-	-	-	-	-	-	-	-	-	-	1.00	0.09
Self-transcendence[b]	-	-	-	-	-	-	-	-	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.4: Bivariate correlations of smoking and alcohol drinking among all subjects

Variable	Smoking (ever)	Smoking (pack-years)	Alcohol use (ever)	Alcohol consumption (drink-years)
PD	-0.03	-0.04	0.05	0.07
Age (Years)	0.08	0.03	0.04	0.12
Sex	-0.15*	-0.15*	-0.17*	-0.22**
Education – highest grade completed	-0.10	-0.14	0.21**	0.04
Neuroticism[a]	-0.10	-0.07	-0.12	-0.06
Extraversion[a]	-0.17*	-0.08	-0.004	-0.02
Openness[a]	-0.02	0.06	0.12	-0.07
Agreeableness[a]	-0.10	-0.16*	-0.11	-0.16*
Conscientiousness[a]	-0.06	0.07	-0.02	0.03
Novelty-seeking[b]	0.04	0.07	0.10	0.05
Harm-avoidance[b]	0.01	-0.07	-0.05	-0.06
Reward dependence[b]	-0.14	-0.22**	-0.10	-0.17*
Persistence[b]	-0.10	-0.04	-0.10	-0.08
Self-directiveness[b]	0.12	0.06	-0.005	-0.01
Cooperativeness[b]	0.03	0.02	-0.13	-0.13
Self-transcendence[b]	-0.07	-0.06	-0.10	-0.21**
Activity Risks (age <35 years)	0.20**	0.24**	0.24**	0.17*
Lifestyle Risks (age <35 years)	0.48**	0.70**	0.24**	0.71**
Routinization (age 20-35 years)	-0.13	-0.20**	-0.19*	0.13
Number of jobs	-0.07	-0.008	-0.0002	-0.004
Number of job categories	0.07	0.13	0.13	0.03
Complexity of work with people[c]	0.08	0.18*	-0.13	-0.09
Complexity of work with data[c]	0.03	0.13	-0.14	-0.09
Complexity of work with things[c]	0.02	-0.09	0.04	0.07
Smoking (ever)	1.00	0.55**	0.08	0.19**
Smoking (pack-years)	-	1.00	0.12	0.18*
Alcohol use (ever)	-	-	1.00	0.24**
Alcohol consumption (drink-years)	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.5: Bivariate correlations of occupational characteristics among all subjects

Variable	Number of jobs	Number of job categories	Complexity of work with people[c]	Complexity of work with data[c]	Complexity of work with things[c]
PD	-0.11	-0.03	0.004	0.03	-0.03
Age (Years)	-0.18*	-0.16*	0.07	0.002	-0.12
Sex	-0.12	-0.14	-0.08	0.17*	0.07
Education – highest grade completed	0.09	-0.04	-0.48**	-0.30**	0.18*
Neuroticism[a]	0.02	-0.04	0.002	-0.003	0.04
Extraversion[a]	0.17*	0.13	-0.07	-0.22**	-0.02
Openness[a]	0.15*	0.10	-0.19**	-0.02	0.06
Agreeableness[a]	-0.04	-0.13	-0.05	-0.02	0.03
Conscientiousness[a]	0.03	0.003	-0.01	-0.09	0.02
Novelty-seeking[b]	-0.05	0.16*	-0.07	0.09	0.04
Harm-avoidance[b]	-0.10	-0.17*	-0.09	0.01	0.02
Reward dependence[b]	-0.10	-0.14	0.02	-0.004	-0.04
Persistence[b]	0.07	0.11	-0.01	-0.02	0.10
Self-directiveness[b]	0.12	0.13	-0.10	-0.05	0.03
Cooperativeness[b]	0.04	0.002	-0.03	-0.04	-0.04
Self-transcendence[b]	0.13	0.09	0.18*	0.04	-0.02
Activity Risks (age <35 years)	0.21**	0.29**	-0.01	-0.10	-0.06
Lifestyle Risks (age <35 years)	0.07	0.20**	0.09	-0.002	-0.05
Routinization (age 20-35 years)	-0.19*	-0.20**	0.01	0.06	-0.01
Smoking (ever)	-0.07	0.07	0.08	0.03	0.02
Smoking (pack-years)	-0.008	0.13	0.18*	0.13	-0.09
Alcohol use (ever)	0.0002	0.02	-0.13	-0.14	0.04
Alcohol consumption (drink-years)	0.0004	0.03	-0.09	-0.09	0.07
Number of jobs	1.00	0.78**	0.05	-0.04	-0.07
Number of job categories	-	1.00	0.08	0.01	-0.05
Complexity of work with people[c]	-	-	1.00	0.43**	-0.34**
Complexity of work with data[c]	-	-	-	1.00	-0.07
Complexity of work with things[c]	-	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.6: Bivariate correlations of early-adult personality traits among cases

Variable	Activity Risks (age <35 years)	Lifestyle Risks (age <35 years)	Routinization (age 20-35 years)
Age (Years)	-0.01	0.02	0.08
Sex	-0.45**	-0.15	0.26*
Education – highest grade completed	0.12	-0.003	-0.16
Neuroticism[a]	-0.24*	-0.11	0.23*
Extraversion[a]	0.20	-0.04	-0.28*
Openness[a]	0.09	0.04	-0.17
Agreeableness[a]	-0.26*	-0.06	0.23*
Conscientiousness[a]	0.02	0.22	0.15
Novelty-seeking[b]	0.28*	0.05	-0.36**
Harm-avoidance[b]	-0.34**	-0.12	0.35**
Reward dependence[b]	-0.32**	-0.16	0.19
Persistence[b]	-0.15	-0.14	0.10
Self-directiveness[b]	0.18	0.11	-0.05
Cooperativeness[b]	-0.17	0.10	0.12
Self-transcendence[b]	-0.05	-0.11	-0.05
Number of jobs	0.22	0.05	-0.22*
Number of job categories	0.27*	0.11	-0.27
Complexity of work with people[c]	-0.08	-0.05	-0.09
Complexity of work with data[c]	-0.05	-0.07	-0.07
Complexity of work with things[c]	-0.03	0.003	0.08
Smoking (ever)	0.17	0.45**	-0.17
Smoking (pack-years)	0.26*	0.67**	-0.26*
Alcohol use (ever)	0.34**	0.25*	-0.20
Alcohol consumption (drink-years)	0.23*	0.70**	0.10
Activity Risks (age <35 years)	1.00	0.35**	-0.66**
Lifestyle Risks (age <35 years)	-	1.00	-0.09
Routinization (age 20-35 years)	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.7: Bivariate correlations of current personality traits among cases

Variable	Neuroticism[a]	Extraversion[a]	Openness[a]	Agreeableness[a]	Conscientiousness[a]	Novelty-seeking[b]	Harm-avoidance[b]	Reward dependence[b]	Persistence[b]	Self-directiveness[b]	Cooperativeness[b]	Self-transcendence[b]
Age (Years)	-0.30**	0.15	-0.41**	0.06	0.13	-0.12	-0.28*	0.21	-0.27*	0.05	-0.13	-0.03
Sex	0.08	-0.003	-0.03	0.33**	0.07	-0.13	0.13	0.30**	0.16	-0.12	0.27*	-0.04
Education – highest grade completed	0.09	0.06	0.44**	0.03	-0.11	0.11	0.15	-0.08	0.16	0.05	-0.03	0.05
Activity Risks (age <35 years)	-0.24*	0.20	0.09	-0.26*	0.02	0.28*	-0.34**	-0.32**	-0.15	0.18	-0.17	-0.05
Lifestyle Risks (age <35 years)	-0.11	-0.04	0.04	-0.06	0.22	0.05	-0.12	-0.16	-0.14	0.11	0.10	-0.11
Routinization (age 20-35 years)	0.23*	-0.28*	-0.17	0.23*	0.15	-0.36**	0.35**	0.19	0.10	-0.05	0.12	-0.05
Number of jobs	0.03	0.12	0.17	0.08	0.06	0.05	-0.007	-0.20	0.02	0.05	0.18	0.10
Number of job categories	-0.02	0.09	0.13	-0.07	0.04	0.09	-0.09	-0.17	-0.01	0.04	0.11	0.03
Complexity of work with people[c]	-0.18	0.01	-0.22*	-0.10	0.04	-0.12	-0.23*	-0.01	-0.05	-0.00005	0.05	0.15
Complexity of work with data[c]	-0.05	-0.23*	0.05	-0.01	0.02	0.17	-0.06	0.05	0.02	0.03	0.07	0.10
Complexity of work with things[c]	0.12	-0.02	-0.09	0.12	0.03	0.02	0.09	0.03	0.07	-0.14	-0.08	-0.12
Smoking (ever)	-0.17	-0.07	-0.02	-0.03	0.01	0.02	-0.02	-0.03	-0.20	0.10	0.10	-0.10
Smoking (pack-years)	-0.10	-0.04	0.08	-0.08	0.13	0.06	-0.07	-0.07	-0.14	0.10	0.19	0.02
Alcohol use (ever)	-0.22*	0.03	0.03	-0.08	0.02	-0.02	-0.05	-0.13	-0.14	0.05	-0.13	-0.10
Alcohol consumption (drink-years)	-0.07	0.04	0.01	-0.07	0.10	0.07	-0.08	-0.16	-0.13	-0.02	-0.02	-0.21
Neuroticism[a]	1.00	-0.52**	0.21	-0.21	-0.46**	0.09	0.72**	-0.03	-0.04	-0.56**	-0.16	0.14
Extraversion[a]	-	1.00	-0.05	0.24*	0.25*	0.11	-0.66**	0.29*	0.26*	0.26*	0.26*	0.21
Openness[a]	-	-	1.00	0.04	0.07	0.36**	0.14	-0.03	0.37**	0.04	0.24*	0.32**
Agreeableness[a]	-	-	-	1.00	0.35**	-0.27*	-0.11	0.49**	0.0006	0.27*	0.59**	-0.03
Conscientiousness[a]	-	-	-	-	1.00	-0.22	-0.43**	0.05	0.40**	0.47**	0.42**	0.07

Table A.7 (Cont)

Variable	Neuroticism[a]	Extraversion[a]	Openness[a]	Agreeableness[a]	Conscientiousness[a]	Novelty-seeking[b]	Harm-avoidance[b]	Reward dependence[b]	Persistence[b]	Self-directiveness[b]	Cooperativeness[b]	Self-transcendence[b]
Novelty-seeking[b]	-	-	-	-	-	1.00	-0.08	-0.18	-0.06	-0.23*	-0.23	0.27*
Harm-avoidance[b]	-	-	-	-	-	-	1.00	-0.09	-0.11	-0.51**	-0.25*	-0.13
Reward dependence[b]	-	-	-	-	-	-	-	1.00	-0.004	0.13	0.44**	0.004
Persistence[b]	-	-	-	-	-	-	-	-	1.00	0.05	0.27*	0.38**
Self-directiveness[b]	-	-	-	-	-	-	-	-	-	1.00	0.39**	-0.12
Cooperativeness[b]	-	-	-	-	-	-	-	-	-	-	1.00	0.08
Self-transcendence[b]	-	-	-	-	-	-	-	-	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.8: Bivariate correlations of smoking and alcohol drinking among cases

Variable	Smoking (ever)	Smoking (pack-years)	Alcohol use (ever)	Alcohol consumption (drink-years)
Age (Years)	0.11	-0.02	0.06	0.10
Sex	-0.11	-0.10	-0.23*	-0.10
Education – highest grade completed	-0.11	-0.08	0.22*	0.07
Neuroticism[a]	-0.17	-0.10	-0.22*	-0.07
Extraversion[a]	-0.07	-0.04	0.03	0.04
Openness[a]	-0.02	0.08	0.03	0.01
Agreeableness[a]	-0.03	-0.08	-0.08	-0.07
Conscientiousness[a]	0.01	0.13	0.02	0.10
Novelty-seeking[b]	0.02	0.06	-0.02	0.07
Harm-avoidance[b]	-0.02	-0.07	-0.05	-0.08
Reward dependence[b]	-0.03	-0.07	-0.13	-0.16
Persistence[b]	-0.20	-0.14	-0.14	-0.13
Self-directiveness[b]	0.10	0.10	0.05	-0.02
Cooperativeness[b]	0.10	0.19	-0.13	-0.02
Self-transcendence[b]	-0.10	0.02	-0.10	-0.21
Activity Risks (age <35 years)	0.17	0.26*	0.34**	0.23*
Lifestyle Risks (age <35 years)	0.45**	0.67**	0.25*	0.70**
Routinization (age 20-35 years)	-0.17	-0.26*	-0.20	0.10
Number of jobs	-0.06	0.14	0.005	-0.03
Number of job categories	0.05	0.24*	0.01	-0.05
Complexity of work with people[c]	0.12	0.21*	-0.15	-0.23*
Complexity of work with data[c]	0.05	0.18	-0.25*	-0.24*
Complexity of work with things[c]	-0.05	-0.15	0.04	0.08
Smoking (ever)	1.00	0.60**	0.15	0.13
Smoking (pack-years)	-	1.00	0.11	0.06
Alcohol use (ever)	-	-	1.00	0.22*
Alcohol consumption (drink-years)	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.9: Bivariate correlations of occupational characteristics among cases

Variable	Number of jobs	Number of job categories	Complexity of work with people[c]	Complexity of work with data[c]	Complexity of work with things[c]
Age (Years)	-0.20	-0.08	0.13	-0.08	-0.12
Sex	-0.18	-0.21*	-0.16	0.19	0.26*
Education – highest grade completed	0.08	-0.04	-0.41**	-0.35**	0.02
Neuroticism[a]	0.03	-0.02	-0.18	-0.05	0.12
Extraversion[a]	0.11	0.09	0.01	-0.23*	-0.02
Openness[a]	0.17	0.13	-0.22*	0.05	-0.09
Agreeableness[a]	0.08	-0.07	-0.10	-0.01	0.12
Conscientiousness[a]	0.07	0.04	0.04	0.02	0.03
Novelty-seeking[b]	0.05	0.09	-0.12	0.17	0.02
Harm-avoidance[b]	-0.007	-0.09	-0.23*	-0.06	0.09
Reward dependence[b]	-0.20	-0.17	-0.01	0.05	0.03
Persistence[b]	-0.02	-0.01	-0.05	0.02	0.07
Self-directiveness[b]	0.05	0.04	-0.00005	0.03	-0.14
Cooperativeness[b]	0.18	0.11	0.05	0.07	-0.08
Self-transcendence[b]	0.10	0.03	0.15	0.10	-0.12
Activity Risks (age <35 years)	0.22	0.28*	-0.08	-0.05	-0.03
Lifestyle Risks (age <35 years)	0.05	0.11	-0.05	-0.07	0.003
Routinization (age 20-35 years)	-0.22*	-0.27*	-0.09	-0.07	0.08
Smoking (ever)	-0.06	0-05	0.12	0.05	-0.05
Smoking (pack-years)	0.14	0.24*	0.21*	0.18	-0.15
Alcohol use (ever)	0.005	0.01	-0.15	-0.25*	0.04
Alcohol consumption (drink-years)	-0.03	-0.05	-0.23*	-0.24*	0.08
Number of jobs	1.00	0.83*	0.09	-0.08	-0.14
Number of job categories	-	-	0.09	-0.00008	-0.13
Complexity of work with people[c]	-	-	1.00	0.44**	-0.31**
Complexity of work with data[c]	-	-	-	1.00	0.02
Complexity of work with things[c]	-	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.10: Bivariate correlations of early-adult personality traits among controls

Variable	Activity Risks (age <35 years)	Lifestyle Risks (age <35 years)	Routinization (age 20-35 years)
Age (Years)	-0.28**	0.11	0.25*
Sex	-0.28**	-0.41**	-0.07
Education – highest grade completed	-0.08	-0.12	-0.13
Neuroticism[a]	-0.15	-0.10	0.14
Extraversion[a]	0.39**	-0.06	-0.41**
Openness[a]	0.13	-0.08	-0.37**
Agreeableness[a]	-0.16	-0.29**	-0.18
Conscientiousness[a]	0.17	-0.06	-0.11
Novelty-seeking[b]	0.32**	0.03	-0.39**
Harm-avoidance[b]	-0.43**	-0.10	0.36**
Reward dependence[b]	0.04	-0.26*	-0.11
Persistence[b]	0.25*	0.04	-0.13
Self-directiveness[b]	0.12	0.09	-0.06
Cooperativeness[b]	0.01	-0.21	-0.21
Self-transcendence[b]	0.16	-0.18	-0.12
Number of jobs	0.19	0.10	-0.14
Number of job categories	0.32**	0.26*	-0.14
Complexity of work with people[c]	0.09	0.21	0.11
Complexity of work with data[c]	-0.16	0.07	0.22*
Complexity of work with things[c]	-0.11	-0.09	-0.10
Smoking (ever)	0.23*	0.50**	-0.10
Smoking (pack-years)	0.22*	0.72**	-0.14
Alcohol use (ever)	0.14	0.23*	-0.20
Alcohol consumption (drink-years)	0.10	0.76**	0.16
Activity Risks (age <35 years)	1.00	0.32*	-0.50**
Lifestyle Risks (age <35 years)	-	1.00	-0.01
Routinization (age 20-35 years)	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.11: Bivariate correlations of current personality traits among controls

Variable	Neuroticism[a]	Extraversion[a]	Openness[a]	Agreeableness[a]	Conscientiousness[a]	Novelty-seeking[b]	Harm-avoidance[b]	Reward dependence[b]	Persistence[b]	Self-directiveness[b]	Cooperativeness[b]	Self-transcendence[b]
Age (Years)	-0.14	-0.21	-0.08	-0.02	-0.23*	-0.31**	-0.04	0.04	-0.38**	-0.03	-0.01	-0.16
Sex	0.19	0.06	0.18	0.33**	0.05	0.11	0.19	0.23*	-0.08	0.01	0.22*	0.06
Education – highest grade completed	-0.23*	0.20	0.54**	0.10	-0.02	0.09	-0.10	-0.10	-0.13	0.20	0.07	-0.18
Activity Risks (age <35 years)	-0.15	0.39**	0.13	-0.16	0.17	0.32**	-0.43**	0.04	0.25*	0.12	0.01	0.16
Lifestyle Risks (age <35 years)	-0.10	-0.06	-0.08	-0.29**	-0.06	0.03	-0.10	-0.26*	0.04	0.09	-0.21	-0.18
Routinization (age 20-35 years)	0.14	-0.41**	-0.37**	-0.18	-0.11	-0.39**	0.36**	-0.11	-0.13	-0.06	-0.21	-0.12
Number of jobs	0.05	0.20	0.09	-0.15	-0.08	0.08	-0.16	-0.01	0.12	0.18	-0.15	0.14
Number of job categories	-0.06	0.14	0.06	-0.18	-0.08	0.23*	-0.23*	-0.11	0.22*	0.23	-0.11	0.14
Complexity of work with people[c]	0.18	-0.13	-0.16	0.0008	-0.05	-0.03	0.04	0.04	0.02	-0.21*	-0.10	0.21*
Complexity of work with data[c]	0.05	-0.21*	-0.09	-0.03	-0.19	0.01	0.07	-0.05	-0.08	-0.13	-0.17	-0.02
Complexity of work with things[c]	-0.03	-0.02	0.19	-0.07	0.02	0.06	-0.06	-0.09	0.13	0.20	-0.01	0.09
Smoking (ever)	-0.02	-0.25*	-0.03	-0.17	-0.12	0.06	0.05	-0.23*	-0.004	0.15	-0.05	-0.03
Smoking (pack-years)	-0.05	-0.10	0.03	-0.23*	0.02	0.09	-0.07	-0.33**	0.03	0.01	-0.13	-0.12
Alcohol use (ever)	-0.05	-0.02	0.22*	-0.12	-0.05	0.18	-0.06	-0.07	-0.08	-0.03	-0.12	-0.08
Alcohol consumption (drink-years)	-0.08	-0.07	-0.14	-0.27**	-0.02	0.01	-0.06	-0.18	-0.03	0.02	-0.25*	-0.21*
Neuroticism[a]	1.00	-0.35*	-0.14	-0.20*	-0.34**	-0.04	0.68**	0.09	-0.05	-0.53**	-0.27*	0.12
Extraversion[a]	-	1.00	0.28*	0.26*	0.48**	0.34**	-0.61**	0.23*	0.37**	0.17	0.12	0.28*
Openness[a]	-	-	1.00	0.10	-0.14	0.29**	-0.24*	-0.01	-0.01	0.03	0.07	0.16
Agreeableness[a]	-	-	-	1.00	0.39**	-0.12	-0.08	0.38**	-0.04	0.17	0.56**	0.14
Conscientiousness[a]	-	-	-	-	1.00	-0.21*	-0.32**	0.19	0.42**	0.39**	0.27*	0.03
Novelty-seeking[b]	-	-	-	-	-	1.00	-0.28**	-0.09	-0.003	-0.18	-0.09	0.16

Table A.11 (Cont)

Variable	Neuroticism[a]	Extraversion[a]	Openness[a]	Agreeableness[a]	Conscientiousness[a]	Novelty-seeking[b]	Harm-avoidance[b]	Reward dependence[b]	Persistence[b]	Self-directiveness[b]	Cooperativeness[b]	Self-transcendence[b]
Harm-avoidance[b]	-	-	-	-	-	-	1.00	-0.05	-0.20	-0.43**	-0.15	-0.17
Reward dependence[b]	-	-	-	-	-	-	-	1.00	0.09	-0.004	0.45**	0.30**
Persistence[b]	-	-	-	-	-	-	-	-	1.00	0.14	-0.18	0.28**
Self-directiveness[b]	-	-	-	-	-	-	-	-	-	1.00	0.34**	-0.14
Cooperativeness[b]	-	-	-	-	-	-	-	-	-	-	1.00	0.08
Self-transcendence[b]	-	-	-	-	-	-	-	-	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.12: Bivariate correlations of smoking and alcohol drinking among controls

Variable	Smoking (ever)	Smoking (pack-years)	Alcohol use (ever)	Alcohol consumption (drink-years)
Age (Years)	0.06	0.07	0.02	0.14
Sex	-0.20*	-0.20*	-0.11	-0.35**
Education – highest grade completed	-0.12	-0.20	0.23*	0.06
Neuroticism[a]	-0.02	-0.05	-0.05	-0.08
Extraversion[a]	-0.25*	-0.10	-0.02	-0.07
Openness[a]	-0.03	0.03	0.22*	-0.14
Agreeableness[a]	-0.17	-0.23*	-0.12	-0.27**
Conscientiousness[a]	-0.12	0.02	-0.05	-0.02
Novelty-seeking[b]	0.06	0.09	0.18	0.01
Harm-avoidance[b]	0.05	-0.07	-0.06	-0.06
Reward dependence[b]	-0.23*	-0.33**	-0.07	-0.18
Persistence[b]	-0.004	0.03	-0.08	-0.03
Self-directiveness[b]	0.15	0.01	-0.03	0.02
Cooperativeness[b]	-0.05	-0.13	-0.12	-0.25*
Self-transcendence[b]	-0.03	-0.12	-0.08	-0.21*
Activity Risks (age <35 years)	0.23*	0.22*	0.14	0.10
Lifestyle Risks (age <35 years)	0.50**	0.72**	0.23*	0.76**
Routinization (age 20-35 years)	-0.10	-0.14	-0.20	0.16
Number of jobs	-0.09	-0.12	0.005	0.05
Number of job categories	0.08	0.06	0.02	0.12
Complexity of work with people[c]	0.05	0.15	-0.11	0.09
Complexity of work with data[c]	0.002	0.09	-0.03	0.15
Complexity of work with things[c]	0.09	-0.04	0.04	0.07
Smoking (ever)	1.00*	0.51**	0.02	0.28**
Smoking (pack-years)	-	1.00	0.13	0.31**
Alcohol use (ever)	-	-	1.00	0.27**
Alcohol consumption (drink-years)	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

Table A.13: Bivariate correlations of occupational characteristics among controls

Variable	Number of jobs	Number of job categories	Complexity of work with people[c]	Complexity of work with data[c]	Complexity of work with things[c]
Age (Years)	-0.14	-0.23*	0.003	0.10	-0.11
Sex	-0.11	-0.09	-0.01	0.17	-0.11
Education – highest grade completed	0.08	0.05	-0.56**	-0.26**	0.31**
Neuroticism[a]	0.05	-0.06	0.18	0.05	-0.03
Extraversion[a]	0.20	0.14	-0.13	-0.21*	-0.02
Openness[a]	0.09	0.06	-0.16	-0.09	0.19
Agreeableness[a]	-0.15	-0.18	0.0008	-0.03	-0.07
Conscientiousness[a]	-0.02	-0.03	-0.05	-0.19	0.02
Novelty-seeking[b]	0.08	0.23*	-0.03	0.01	0.06
Harm-avoidance[b]	-0.16	-0.24*	0.04	0.07	-0.06
Reward dependence[b]	-0.01	-0.11	0.04	-0.05	-0.09
Persistence[b]	0.12	0.22*	0.02	-0.08	0.13
Self-directiveness[b]	0.18	0.23	-0.21*	-0.13	0.20
Cooperativeness[b]	-0.15	-0.11	-0.10	-0.17	-0.01
Self-transcendence[b]	0.14	0.14	0.21*	-0.02	0.09
Activity Risks (age <35 years)	0.19	0.32**	0.09	-0.16	-0.11
Lifestyle Risks (age <35 years)	0.10	0.26*	0.21	0.07	-0.09
Routinization (age 20-35 years)	-0.14	-0.14	0.11	0.22*	-0.10
Smoking (ever)	-0.09	0.08	0.05	0.002	0.09
Smoking (pack-years)	-0.12	0.06	0.15	0.09	-0.04
Alcohol use (ever)	0.006	0.02	-0.11	-0.03	0.04
Alcohol consumption (drink-years)	0.05	0.12	0.09	0.15	0.07
Number of jobs	1.00	0.74**	0.03	0.08	0.03
Number of job categories	-	1.00	0.08	0.06	0.01
Complexity of work with people[c]	-	-	1.00	0.44**	-0.36**
Complexity of work with data[c]	-	-	-	1.00	-0.18
Complexity of work with things[c]	-	-	-	-	1.00

[a] Current traits as measured by NEO
[b] Current traits as measured by TCI
[c] Primary lifetime occupation
* $p<0.05$
** $p<0.01$

About the Author

Kelly L. Sullivan received a BSW from the University of West Florida in 2000, a MSPH from the University of South Florida and a PhD from the University of South Florida. She has been a faculty member in the Department of Neurology at the University of South Florida since 2004 and recently joined the College of Nursing at the University of South Florida. As an author of over 40 peer-reviewed manuscripts, she has conducted numerous research studies including sponsored and investigator initiated clinical trials.