

Psychological Characteristics and Subjective Intolerance for Xenobiotic Agents of Normal Young Adults with Trait Shyness and Defensiveness

A Parkinsonian-like Personality Type?

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The present study examines the psychological characteristics and self-reported responses to xenobiotic agents such as tobacco smoke and pesticide of normal young adults with personality traits similar to those claimed for Parkinsonian patients. Previous research, though controversial, has suggested that persons with idiopathic Parkinson's disease (PD) have premorbid personality traits that may include shyness and repressive defensiveness. Other epidemiological evidence indicates that PD patients may have premorbidly increased prevalence of anxiety, affective, and/or somatoform disorders; decreased rates of smoking and alcohol consumption; and elevated exposure to herbicides or pesticides. A total of 783 college students enrolled in an introductory psychology course completed the Cheek-Buss Scale (shyness), the Marlowe-Crowne Social Desirability Scale (defensiveness), Symptom Checklist 90 (revised), the Mastery Scale, a health history checklist, and rating scales for frequency of illness from alcohol and 10 common environmental chemicals. Subjects were divided into four groups on the basis of above- versus below-median scores on the Cheek-Buss and Marlowe-Crowne scales (persons high in shyness and defensiveness, those high only in shyness, those high only in defensiveness, and those low in both shyness and defensiveness). The group high in shyness but low in defensiveness had the highest, whereas the group low in shyness but high in defensiveness had the lowest, total scores on the SCL-90-R; the two shyest groups were lowest in sense of mastery. Similar to PD, the group high in both shyness and defensiveness overall reported the least number of smokers (10% *vs.* 19% in those high only in shyness, 17% in those high only in defensiveness, and 28% in those low in both traits, $p < .001$); differences within women largely accounted for this finding. Subjects higher in shyness and/or defensiveness rated themselves higher in frequency of illness from a small amount of alcohol than did those who were low in both shyness and defensiveness. The group who was high in both shyness and defensiveness tended to report the highest frequency of illness from pesticide as well as other xenobiotic odors (*e.g.*, newsprint). Taken together with previous research, the findings suggest that certain young adults high in shyness, and especially those also high in defensiveness, may be among the subset of the population at increased risk for PD later in life.

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The recent discovery of treatments such as selegiline (L-deprenyl) to slow progression of idiopathic Parkin-

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son's disease (PD) has increased the need for early detection of individuals at risk (Parkinson's Study Group, 1993; Tetrad and Langston, 1989). Premorbid personality traits (Paulson and Dadmehr, 1991; Todes and Lees, 1985) as well as certain psychiatric (anxiety, depression) and psychophysiological (hysteria, irritable bowel) disorders (Bell et al., 1993b; Cummings, 1992; Rajput et al., 1987) are among the factors that have been associated with increased risk of developing PD later in life. In particular, the so-called premorbid "Parkinsonian personality" (Golbe and Langston, 1993;

Paulson and Dadmehr, 1991; Todes and Lees, 1985), though still controversial (Riklan et al., 1959), encompasses descriptors that personality researchers might cluster into two primary traits: a) shyness ("introverted," "shy," "timid," "subordinate," "less outgoing," "nervous") (Duvoisin et al., 1981; Paulson and Dadmehr, 1991; Poewe et al., 1983) and b) repressive defensiveness ("responsible," "morally rigid," "law abiding") (Paulson and Dadmehr, 1991; Poewe et al., 1983). Such a conceptualization has the advantage of facilitating application of standardized psychological scales to research in PD. For example, Bell et al.⁵ recently found that 17% of community elderly scoring in the top quartile for shyness on the Cheek-Buss Shyness scale (Cheek and Buss, 1981) versus only 2% of those in the bottom quartile reported family members with PD diagnoses. Given prior evidence for familial vulnerability to shyness (Kagan et al., 1991), the latter observation provides additional, albeit indirect, support for the hypothesis that shyness may be a risk factor for PD.

Shyness is a temperamental trait that involves behavioral and physiological hyperreactivity to the novel and unfamiliar (Kagan et al., 1987). An elegant series of studies by Kagan and colleagues has demonstrated that extremely shy infants are prone to colic, constipation, nasal allergies, and insomnia (Kagan, 1992; Kagan et al., 1987, 1988, 1991); those who remain extremely shy or behaviorally inhibited throughout early childhood develop clinical anxiety disorders (Hirshfeld et al., 1992; Reznick et al., 1992; Rosenbaum et al., 1992). Patients with diagnoses of panic disorder and agoraphobia have a much higher proportion of behaviorally inhibited offspring than do normal controls (Rosenbaum et al., 1988). Shy young and older adults are also more anxious and depressed than their more outgoing peers (Bell, 1992; Bell et al., 1990, 1993c; Biederman et al., 1990; Kagan et al., 1991). Thus, the psychopathological features of shyness are consistent with the increased relative risk for PD in persons with premorbid anxiety and affective disorders (Rajput et al., 1987).

In addition to shyness, trait defensiveness emerges as a possible characteristic of PD patients, who have been described as overcontrolled, inflexible, law abiding, and moralistic (Poewe et al., 1983; Todes and Lees, 1985). Defensiveness is the tendency to avoid social disapproval and to present oneself consciously and unconsciously in the most positive possible way; this personality feature strongly favors self-reports of strict adherence to social norms and legal rules (Jamner et al., 1988; Weinberger, 1990). Although defensive individuals report lower rates of lifetime psychiatric diagnoses

(Lane et al., 1990) and lower levels of negative affect in experimental settings (Weinberger, 1990; Weinberger et al., 1979), physiological studies indicate that defensiveness facilitates increased cardiovascular reactivity under stress. The degree of sympathetic nervous system activation in highly defensive persons who deny anxiety often matches that in nondefensive individuals who acknowledge high anxiety (Weinberger et al., 1979). Consequently, defensiveness might amplify physiological hyperreactivity from shyness in vulnerable persons, as it has already been shown to do for type A cynical hostility (Jamner et al., 1991). If so, then the traits of shyness and defensiveness, especially in combination, might indicate a heightened premorbid reactivity of neurobehavioral and neurophysiological functions in those prone to develop PD.

In PD, numerous investigators have focused epidemiological and preclinical studies on possible endogenous (*e.g.*, dopamine, cysteine: Cawley and Shickley, 1992; Olney et al., 1990) and/or exogenous (*e.g.*, MPTP, herbicides, pesticides, n-hexane: Brandt et al., 1990; Corsini et al., 1985; Heikkila et al., 1985; Pezzoli et al., 1990; Semchuk et al., 1992) neurotoxicants that might damage dopaminergic pathways in vulnerable individuals. At the same time, many, but not all, investigators have noted that PD patients have paradoxically lower rates of premorbid smoking and drinking histories (Golbe and Langston, 1993; Paulson and Dadmehr, 1991; Pollock and Hornabrook, 1966), despite their apparently elevated levels of anxiety and dysphoria. Within low defensive community elderly, Bell et al.⁶ demonstrated that those who are high in shyness ingest a significantly smaller percentage of their calories from alcohol than do those who are low in shyness. Shyness in younger and older adults is also associated with the symptom of *cacosmia* (Bell et al., 1993d, 1993e, 1994), *i.e.*, the subjective sense of feeling ill (*e.g.*, headache, nausea, dizziness) from the odor of low levels of environmental chemicals that have no effect on normal subjects (Ryan et al., 1988). Among high defensive patients of mixed ages, Jamner et al. (1988) found decreased rates of use and increased rates of intolerance (hives, itching, nausea) for opiate drugs. Taken together, these data raise the possibility that if a pre-PD personality exists, at least a subset of individuals with such traits might also exhibit premorbid anomalies in responses to some xenobiotic substances (Bell et al., 1993e), including certain drugs, foods,⁶ and/or environmental chemicals.

Retrospective studies of personality after emergence of PD symptoms are usually criticized for a potential illness-related distortion of recall for premorbid status

⁵Bell IR, Amend D, Kaszniak AW, Schwartz GE, Peterson JM, Stini WA, Miller JW, Selhub J (1994) *Trait shyness in the elderly: Evidence for an association with Parkinson's disease in family members and biochemical correlates*. Submitted for publication.

⁶Bell IR, Schwartz GE, Meredith KE, Ritenbaugh C, Graver E, Martino GM (1994) *Self-reported eating habits for fats and sweets: Relationship to distress, repression, and shyness in older adults*. Submitted for publication.

in both patients and their significant others (Paulson and Dadmehr 1991; Riklan et al., 1959; Todes and Lees, 1985). However, if certain personality traits precede PD, then persons with these same characteristics but without PD should exhibit some of the same descriptive premorbid features of PD. As a first step, the purpose of the present study was to compare young adults who were relatively higher versus lower in shyness and defensiveness with regard to psychological profiles and responses to xenobiotics.

Method

Subjects

The subjects were college students of both sexes enrolled in the introductory psychology course at the University of Arizona (different cohort from all previously reported student samples studied by Bell et al., 1990, 1993d, 1993e). Information on age and gender, but not racial/ethnic background, was requested. Subjects received course credit for their participation.

Questionnaires

The questionnaires for this study included the Cheek-Buss Shyness Scale (Cheek and Buss, 1981), the Marlowe-Crowne Social Desirability Scale (Crowne and Marlowe, 1960), Pearlin-Schooler Mastery Scale (1978), SCL-90-R (Derogatis, 1975), a checklist of physician-diagnosed psychiatric and medical disorders, and ratings of frequency of illness on a 5-point Likert scale (1 = almost never, 5 = almost always) for illness from a small amount of alcohol, tobacco smoke, pesticide, drying paint, fresh tar, household disinfectants, fresh newsprint, perfume, new carpet, car exhaust, and natural gas. Subjects were asked whether or not they currently smoke cigarettes. To screen for subjective cognitive problems (Rajput et al., 1993), an additional scale included 20 items on subjective symptoms of memory and concentration difficulties, each rated for frequency on a 5-point Likert scale (1 = almost never, 5 = almost always; higher scores indicate greater cognitive dysfunction). Items in this scale have been found previously to differentiate patients with extreme cacosmia from normal subjects (Miller and Mitzel, unpublished observations), *e.g.*, "I have trouble recalling an unfamiliar telephone number that I have just dialed," "I forget where I parked my car," and "I tend to be clumsy."

The Cheek-Buss Scale is a 9-item (each item rated on a 5-point Likert scale) reliable and valid measure of shyness that correlates with ratings by blind judges of videotaped behavioral observations. The Marlowe-Crowne Scale (Crowne and Marlowe, 1960) is a 33-item true/false validated scale derived from the Minnesota Multiphasic Personality Inventory that taps the dimension of repressive defensiveness as described above.

The Marlowe-Crowne may identify two different aspects of defensiveness: a) avoidance of threats to self-esteem and b) attention to minimization of negative impressions by other people (Warrenburg et al., 1989). The Mastery Scale is a 7-item reliable and valid measure of sense of control over one's own fate; each item is rated on a 4-point scale (1 = strongly agree to 4 = strongly disagree; high scores indicate greater mastery). The SCL-90-R is a 90-item scale (each item rated on a 5-point Likert scale from 0 = not at all to 4 = extremely) capable of generating a total symptom score as well as nine primary subscale scores.

Subjects were assigned to one of four groups (HISHY/HIDEF = above median shyness/above median defensiveness; HISHY/LODEF = above median shyness/below median defensiveness; LOSHY/HIDEF = below median shyness/above median defensiveness; LOSHY/LODEF = below median shyness/below median defensiveness) based on scores above or below the median for two of the scales, the Cheek-Buss Shyness and Marlowe-Crowne questionnaires (respective sample medians, 15 and 16). Statistical analyses included analyses of variance and covariance and chi-square tests.

Results

A total of 783 students (mean age, 18.8 ± 2.6 years; 59.6% women and 40.4% men) completed the questionnaires. The overall sample included 18% current smokers, and 2.4% had physician diagnoses of anxiety, 0.4% of panic disorder (all three cases in the HISHY groups), 4.4% of depression, and 2.2% of irritable bowel. Mean subjective cognitive dysfunction score was 32.0 ± 7.4 . The four personality groups did not differ for age, but did for gender distribution (HISHY/HIDEF, $N = 193$, 59.1%F; HISHY/LODEF, $N = 233$, 52.2%F; LOSHY/HIDEF, $N = 225$, 65.6%F; LOSHY/LODEF, $N = 132$, 62.9%F; $\chi^2 [3] = 9.3$, $p = .03$).

Table 1 and Figure 1 summarize the group differences for the SCL-90-R total and subscale scores. As expected from previous studies of defensiveness (Lane et al., 1990), the LOSHY/HIDEF group generally had the lowest ratings for SCL-90-R and the highest for Mastery Scale scores. The HISHY/LODEF group was higher for most subscales as well as on the general severity index (measure of number of symptoms and intensity of distress; Figure 1) than were the other three groups. Both HISHY groups were lower in Mastery than were the normal subjects (LOSHY/LODEF). All of these group differences remained significant after covarying for gender. The HISHY groups had the most anxiety diagnoses (HISHY/HIDEF 3.1%, HISHY/LODEF 4.3%, LOSHY/HIDEF 0%, LOSHY/LODEF 2.3%; $\chi^2 [3] = 9.4$, $p = .02$), but did not differ significantly for panic disorder, depression, or irritable bowel (all $p > .10$). Groups

TABLE 1
Personality Group Differences for SCL-90-R and Mastery Scales^a

	Personality Group			
	HISHY/HIDEF (N = 193)	HISHY/LODEF (N = 233)	LOSHY/HIDEF (N = 225)	LOSHY/LODEF (N = 132)
SCL-90-R scales				
Grand total	62.8 ± 49.3	81.6 ± 55.7	40.6 ± 37.3	60.3 ± 44.9****
Somatization	7.6 ± 7.0	9.6 ± 7.6	6.1 ± 5.9	8.5 ± 7.2****
Obsessive-compulsive	8.6 ± 6.5	11.4 ± 7.8	5.8 ± 5.8	8.5 ± 6.8****
Interpersonal sensitivity	9.6 ± 6.9	12.1 ± 7.6	5.1 ± 4.8	7.7 ± 6.4****
Depression	10.4 ± 8.8	13.8 ± 10.1	7.1 ± 7.4	9.1 ± 7.8****
Anxiety	6.5 ± 6.2	8.0 ± 6.6	4.2 ± 4.4	6.3 ± 5.5****
Hostility	3.7 ± 3.9	5.4 ± 4.8	2.3 ± 3.3	4.3 ± 4.0****
Phobic anxiety	3.0 ± 4.6	3.0 ± 4.1	1.0 ± 2.1	1.8 ± 2.8****
Paranoid ideation	4.7 ± 4.3	6.2 ± 4.9	2.9 ± 3.4	4.6 ± 4.6****
Psychoticism	4.8 ± 5.6	6.8 ± 7.0	2.7 ± 4.1	4.4 ± 5.3****
Pearlin-Schooler Mastery Scale	20.9 ± 3.6	20.6 ± 3.7	23.9 ± 3.9	22.4 ± 4.2****

^aData are expressed as mean ± SD. Analyses of covariance with gender as covariate were used to compare groups. Main effect for personality group: **** $p < .0001$.

higher in shyness and/or defensiveness had increased rates of self-reported sneezing and runny/itchy noses when around pollen, dust, molds, or animals (HISHY/HIDEF 57%, HISHY/LODEF 59%, LOSHY/HIDEF 57%, LOSHY/LODEF 45%; $\chi^2[3] = 7.7, p = .05$).

As predicted from studies of PD, the HISHY/HIDEF subjects had the smallest proportion of current smokers (Figure 2). When gender differences between groups were controlled, the differences for smokers remained significant for women, but not for men (women only: HISHY/HIDEF 7.9%, HISHY/LODEF 17.5%, LOSHY/HIDEF 17.7%, LOSHY/LODEF 26.8%; $\chi^2[3]=12.5, p = .006$; men only: HISHY/HIDEF 12.7%, HISHY/LODEF 20.7%, LOSHY/HIDEF 16.9%, LOSHY/LODEF 28.6%; $\chi^2[3] = 5.4, p > .10$). The HISHY/HIDEF group had the highest, and the LOSHY/LODEF had the lowest, ratings for frequency of illness from a small amount of alcohol (Figure 3), a main effect for group membership that remained significant even after analysis of covariance controlling for the significant covariates of gender and SCL-90-R total score (both $p < .0001$)

and the nonsignificant covariate of Mastery score. Table 2 and Figure 4 summarize group differences for illness ratings from the odor of the 10 xenobiotic agents. After covarying for gender, SCL-90-R total score, and Mastery score, the HISHY/HIDEF group remained significantly higher in illness from fresh newspaper (Figure 4), with trends for pesticide, drying paint, and disinfectants but not for tobacco smoke, perfume, new carpet, car exhaust, or natural gas (Table 2). Fresh tar was the only item out of 10 for which the LOSHY/LODEF group showed a trend toward the highest illness score. The HISHY groups indicated that they considered themselves especially sensitive to certain chemicals within women (women only: HISHY/HIDEF 31%, HISHY/LODEF 36%, LOSHY/HIDEF 24%, LOSHY/LODEF 21%; $\chi^2[3] = 7.7, p = .05$), but not men ($p > .10$).

Finally, the groups differed significantly for cognitive dysfunction score (HISHY/HIDEF 31.4 ± 6.8 ; HISHY/LODEF 34.0 ± 7.5 ; LOSHY/HIDEF 29.4 ± 6.7 ; LOSHY/LODEF 32.8 ± 7.8); the HISHY/LODEF group was highest on this variable. As expected (Jamner et al., 1988;

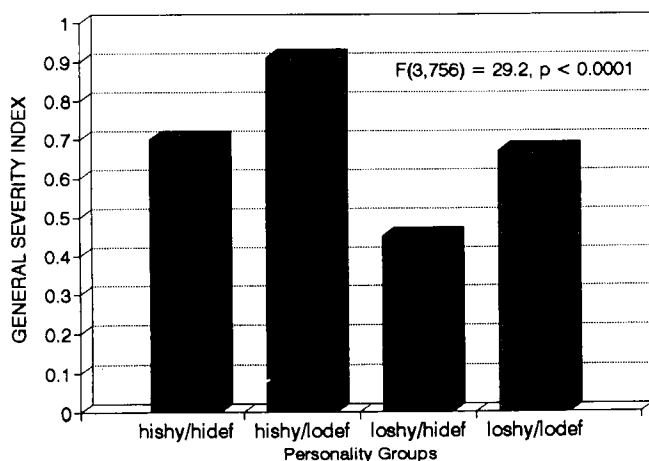


FIG. 1. Personality group differences on SCL-90-R general severity index.

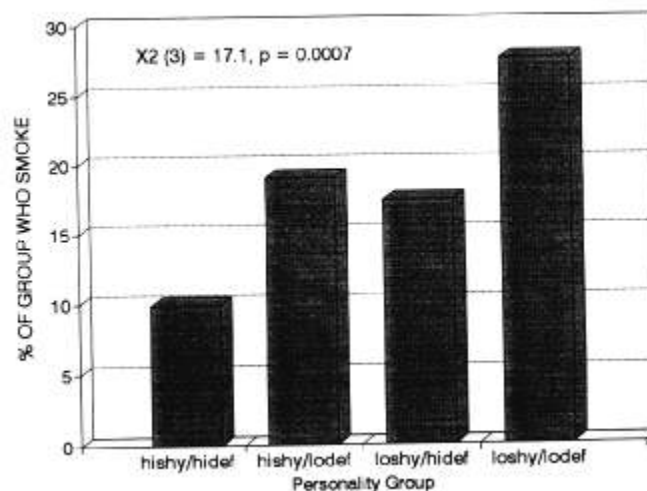


FIG. 2. Percentage of smokers by group.

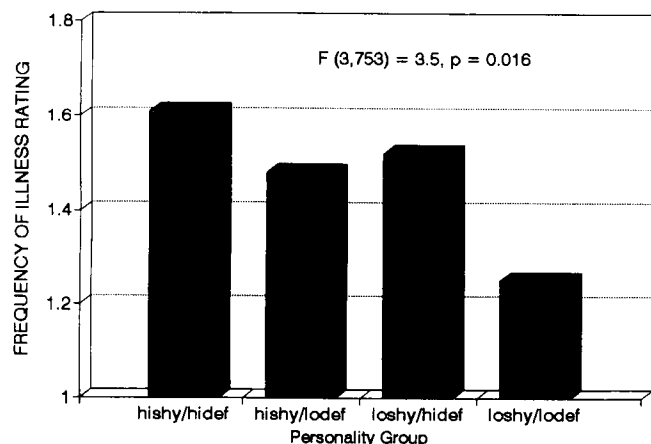


FIG. 3. Illness rating from a small amount of alcohol.

Lane et al., 1990), the LOSHY/HIDEF group was lowest among the groups in rating cognitive difficulties. The group differences remained significant ($F[3,748] = 3.6$, $p = .014$) after covarying for gender ($p = .038$), SCL-90-R total score ($p < .0001$), and Mastery score ($p > .20$).

Discussion

The present findings are consistent with the hypothesis that individuals with premorbid shyness, especially in combination with defensiveness, who report decreased rates of smoking and increased degrees of alcohol intolerance, may be at increased risk for Parkinson's disease (Duvoisin et al., 1981; Golbe and Langston, 1993; Paulson and Dadmehr, 1991; Poewe et al., 1983). The increased psychopathology on the SCL-90-R in the shy groups in the present study as well as in previous research might coincide with the elevated relative risk of PD from premorbid anxiety, affective, and somatoform disorders (Rajput et al., 1987). However, it is the interaction of defensiveness with shyness that maximizes the characteristics of non-smoking and subjective intolerance of xenobiotic agents in the present sample. The group differences for

current smoking habits of these young adults (*i.e.*, the shy-defensive subjects reported the lowest proportion of smokers) strikingly overlap similar epidemiological evidence in PD (Baron, 1986; Golbe and Langston, 1993).

In addition, the data offer support for the possibility of heightened intolerance of certain xenobiotic agents in individuals high in shyness and defensiveness, including beverage alcohol and the odors of newsprint, pesticide, paint, and disinfectants. As in previous research (Bell et al., 1993a, 1993d, 1993e, 1993f, 1994; Morrow et al., 1990, 1991), the latter findings persist or remain strong trends even after controlling for differences in gender distribution and psychological variables between groups. The HISHY/HIDEF group may have the highest rates of intolerance to various exogenous substances; in an earlier college student study, Bell et al. (1993e) found that HISHY/HIDEF subjects reported an increased frequency of illness from both environmental chemicals and common foods. Shy elderly, who have increased rates of PD in their families, also have higher total ratings of illness from xenobiotics than do nonshy elderly.⁵ The present pattern of illness from xenobiotics, despite the lack of significant group differences for illness from tobacco smoke per se in the present study, bolsters the possibility that environmental toxicants may play a role in the development of neuronal damage in PD by synergism with age and additional risk factors. Steventon et al. (1989), for example, have shown that PD patients are impaired in their ability to metabolize certain sulfur-containing drugs. Furthermore, Bell et al.⁵ also have preliminary evidence, for example, for higher plasma levels of the endogenous sulfur-containing excitatory amino acid, L-cysteine, in depressed elderly who report childhood shyness than in depressed elderly without childhood shyness. Cysteine is elevated in PD and other neurodegenerative disorders (Heafield et al., 1990; Olney et al., 1990).

However, the current study has several limitations.

TABLE 2

Personality Group Differences for Ratings of Frequency of Illness from the Odors of Xenobiotic Agents (Cacosmia)^a

	Personality Group			
	HISHY/HIDEF (N = 193)	HISHY/LODEF (N = 233)	LOSHY/HIDEF (N = 225)	LOSHY/LODEF (N = 132)
Tobacco smoke	2.7 ± 1.5	2.4 ± 1.4	2.6 ± 1.5	2.4 ± 1.6
Pesticide	2.0 ± 1.2	1.8 ± 1.1	1.9 ± 1.2	1.8 ± 1.1 [†]
Drying paint	1.7 ± 1.0	1.6 ± 0.9	1.5 ± 0.9	1.5 ± 0.9 [†]
Fresh tar	1.9 ± 1.2	1.8 ± 1.1	1.9 ± 1.3	2.0 ± 1.3 [†]
Disinfectants	1.6 ± 1.0	1.4 ± 0.8	1.4 ± 0.9	1.5 ± 0.9 [†]
Perfume	1.7 ± 1.0	1.7 ± 1.1	1.5 ± 1.0	1.5 ± 0.9
New carpet	1.3 ± 0.7	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6
Car exhaust	2.2 ± 1.2	2.2 ± 1.3	2.2 ± 1.3	2.1 ± 1.3
Natural gas	1.7 ± 1.0	1.7 ± 1.0	1.6 ± 1.1	1.6 ± 1.1

^aData are expressed as mean ± SD. Analyses of covariance with gender, SCL-90-R grand total score, and Mastery score as covariates were used to compare groups.

Main effect for personality group: [†].05 < p < .10.

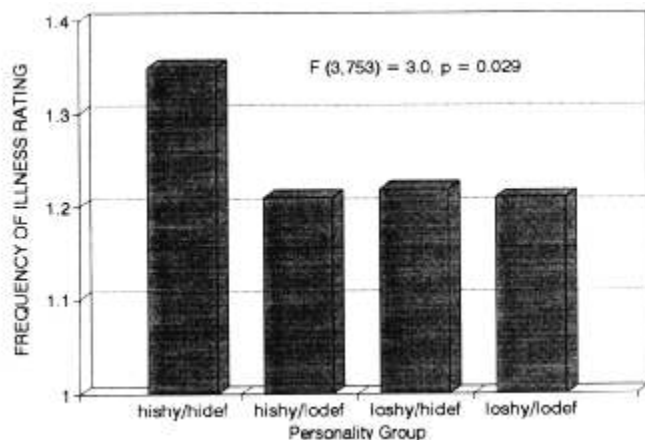


FIG. 4. Illness rating from the odor of fresh newsprint.

First, there is no direct evidence that specific members of the present personality groups will go on to develop PD. At best, these findings in a young, medically uncomplicated sample can provide a rationale for subsequent personality studies in older populations, perhaps with other risk factors for PD. Second, the data rely on self-report. Objective verification of both personality style and psychophysiological correlates by controlled laboratory observations, such as [^{18}F]dopa positron emission tomography studies of nigrostriatal pathways (Salwe et al., 1992), will be essential for future replication and extension of the current findings. Third, the present use of median splits may have weakened power for finding larger group differences in certain variables, such as illness from specific chemical odors. Use of medians optimizes group sample sizes and is consistent with research approaches in related health psychology areas (e.g., Jamner et al., 1991). At the same time, it may be those from the extremes of shyness (Kagan, 1992) and/or defensiveness in the population, not simply those above or below median, who have the greatest potential for clinically significant adverse health outcomes over time. Fourth, previous research on personality and alcoholism suggests that a subset of shy defensive persons may be more, rather than less, vulnerable to alcohol abuse, with loss of control during drinking binges (Cloninger, 1987; Cloninger et al., 1988). The latter findings would seem counterintuitive to the xenobiotic intolerance of the same personality type in the present study as well as to the decreased pre-morbid smoking and alcohol use in PD. Further investigation of additional personality features (Caliri and Golbe, 1992) and/or biochemical characteristics of specific shy defensive individuals with and without PD and with and without alcoholism may be necessary to resolve this apparent contradiction.

Despite these caveats, if shyness is involved in predisposing to PD, then the olfactory system status may provide important clues to underlying pathophysiological

processes (Bell et al., 1992, 1994; Doty et al., 1984). That is, Herbener et al. (1989) have demonstrated slightly above-normal olfactory sensory detection threshold abilities in extremely shy young men. In contrast, patients with PD exhibit objective anosmia (Doty et al., 1992; Ward et al., 1983) as well as decreased cacosmia (Bell et al., 1993b). If these observations are replicated and extended to longitudinal studies of olfaction in shy elderly who develop PD, then it would be heuristically useful to consider the possibility of a transition from olfactory pathway hyperreactivity to hypo-reactivity because of age and other factors. One mechanism by which neuronal hyperactivity might lead to cell loss would be via overactivation by endogenous excitatory amino acids (Sapolsky, 1992). Excitatory amino acids may participate in the MPTP model for Parkinsonian neurodegeneration (Iversen et al., 1992; Turski et al., 1991). Notably, excitatory amino acids play a role in both limbic kindling (Gilbert, 1988) and time-dependent sensitization (Snyder-Keller, 1991). Partial limbic kindling of amygdala, which is a major way station for input from the olfactory bulb, is the animal model for shyness (Adamec, 1990); and time-dependent sensitization in dopaminergic pathways is an animal model for amplified reactivity to stress and to exogenous substances (Antelman, 1988; Antelman et al., 1992a, 1992b; Bell et al., 1993f; Carey, 1993; Hooks et al., 1992; Kalivas, 1993; Post, 1992; Robinson et al., 1982). Consistent with the present findings on gender and smoking, heightened susceptibility to time-dependent sensitization depends in part on female gender (Robinson and Becker, 1986; Robinson et al., 1982) and on increased hyperreactivity to novelty (Hooks et al., 1992) (*cf.*, shyness). Novel chemical odors, as well as other environmental stimuli, can trigger increases in striatal dopaminergic activity of animals (Keller et al., 1983, 1992; Snyder-Keller, 1991) as well as in electrical activity of olfactory and limbic pathways (Bokina et al., 1976). Pesticide overexposures, which have been suspected but not always found as risk factors for PD (Koller et al., 1990; Semchuk et al., 1992), can also facilitate limbic kindling and sensitization (Gilbert, 1992). Thus, inherent hyperreactivity to environmental stressors as well as to even low level xenobiotic agents (Bokina, et al., 1976; Mansour et al., 1981; Wallace, 1991) might favor a neurotoxic outcome in extremely shy persons by excessively mobilizing excitatory amino acids, which would in turn interact with other risk factors, including age to cause neurodegenerative events (Bell et al., 1993a, 1993f, 1994; Coyle and Puttfarcken, 1993). Alternatively, shyness and defensiveness might reflect endogenous individual differences in biochemical capacity to detoxify certain xenobiotics (Mutti and Franchini, 1987; Pezzoli et al., 1990; Seegal and Shain, 1992; Steventon et al., 1989).

Conclusions

Thus, the controversial hypothesis of premorbid Parkinsonian personality traits, *i.e.*, shyness and defensiveness (*cf.*, Duvoisin et al., 1981; Paulson and Dadmehr, 1991; Poewe et al., 1983), if confirmed in case-controlled and longitudinal studies, might provide new avenues for research into specific xenobiotic factors and neurophysiological mechanisms of PD as well as into preventive behavioral interventions. Apart from etiological considerations, however, the present data are consistent with the eventual possibility of identifying persons at risk for PD during preclinical stages (Sawle et al., 1992), when early intervention with currently available treatments might greatly improve and prolong quality of life. On the latter basis alone, shyness and defensiveness merit further examination as possible risk factors for PD.

References

- Adamec RE (1990) Does kindling model anything clinically relevant? *Biol Psychiatry* 27:249-279.
- Antelman SM (1988) Time-dependent sensitization as the cornerstone for a new approach to pharmacotherapy: Drugs as foreign/stressful stimuli. *Drug Dev Res* 14:1-10.
- Antelman SM, Caggiula AR, Knopf S, Kocan DJ, Edwards DJ (1992a) Amphetamine or haloperidol 2 weeks earlier antagonized the plasma corticosterone response to amphetamine; Evidence for the stressful/foreign nature of drugs. *Psychopharmacology* 107:331-336.
- Antelman SM, Kocan D, Knopf S, Edwards DJ, Caggiula AR (1992b) One brief exposure to a psychological stressor induces long-lasting, time-dependent sensitization of both the cataleptic and neurochemical responses to haloperidol. *Life Sci* 51:261-266.
- Baron JA (1986) Cigarette smoking and Parkinson's disease. *Neurology* 36:1490-1496.
- Bell IR (1992) Allergies, physical irritants, depression, and shyness. *J Appl Dev Psychol* 13:125-133.
- Bell IR, Amend D, Kaszniak AW, Schwartz GE (1993a) Memory deficits, sensory impairment, and depression in the elderly. *Lancet* 341:62.
- Bell IR, Dalby P, Amend D, Montgomery EB, Schwartz GE, Peterson JM, Stini W (1993b) Irritable bowel and specific food intolerances in Parkinson's disease. *J Am Coll Nutr* 12:615.
- Bell IR, Jasnosi ML, Kagan J, King DS (1990) Is allergic rhinitis more frequent in young adults with extreme shyness? A preliminary survey. *Psychosom Med* 52:517-525.
- Bell IR, Martino GM, Meredith KE, Schwartz GE, Siani MM, Morrow FD (1993c) Vascular risk factors, urinary free cortisol, and health histories in older adults: Shyness and gender interactions. *Biol Psychol* 35:37-49.
- Bell IR, Miller CM, Schwartz GE (1992) An olfactory-limbic model of multiple chemical sensitivity syndrome: Possible relationships to kindling and affective spectrum disorders. *Biol Psychiatry* 32:218-242.
- Bell IR, Schwartz GE, Amend D, Peterson JM, Stini WA (in press) Sensitization to early life stress and response to chemical odors in older adults. *Biol Psychiatry*.
- Bell IR, Schwartz GE, Peterson JM, Amend D (1993d) Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. *Arch Environ Health* 48:6-13.
- Bell IR, Schwartz GE, Peterson JM, Amend D (1993e) Symptom and personality profiles of young adults from a college student population with self-reported illness from foods and chemicals. *J Am Coll Nutr* 12:693-702.
- Bell IR, Schwartz GE, Peterson JM, Amend D, Stini WA (1993f) Possible time-dependent sensitization to xenobiotics: Self-reported illness from chemical odors, foods, and opiate drugs in an older adult population. *Arch Environ Health* 48:315-327.
- Biederman J, Rosenbaum JF, Hirshfeld DR, Faraone SV, Bolduc EA, Gersten M, Meminger SR, Kagan J, Snidman N, Reznick JS (1990) Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. *Arch Gen Psychiatry* 47:21-26.
- Bokina AI, Eksler ND, Semenenko AD, Merkuryeva RV (1976) Investigation of the mechanism of action of atmospheric pollutants on the central nervous system and comparative evaluation of methods of study. *Environ Health Perspect* 13:37-42.
- Brandt I, Brittebo EB, Feil VJ, Bakke JE (1990) Irreversible binding and toxicity of the herbicide dichlobenil (2,6-dichlorobenzonitrile) in the olfactory mucosa of mice. *Toxicol Appl Pharmacol* 103:491-501.
- Caliri AM, Golbe LI (1992) Olfactory and personality tests as premorbid screening for Parkinson's disease (PD). *Neurology* 42(Suppl 3):440.
- Carey RJ (1993) Motoric sensitization and levodopa accumulation after chronic levodopa treatment in an animal model of Parkinson's disease. *J Geriatr Psychiatry Neurol* 6:152-160.
- Cawley TA, Shickley TJ (1992) The potential neurotoxin 2-OH-dopamine is an inhibitor of arylsulfatase. *Ann NY Acad Sci* 648:256-259.
- Cheek JM, Buss AH (1981) Shyness and sociability. *J Pers Soc Psychol* 41:330-339.
- Cloninger CR (1987) Neurogenetic adaptive mechanisms in alcoholism. *Science* 235:410-416.
- Cloninger CR, Sigvardsson S, Bohman M (1988) Childhood personality predicts alcohol abuse in young adults. *Alcoholism* 12:494-505.
- Corsini GU, Pintus S, Chiueh CC, Weiss JF, Kopin IJ (1985) 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in mice is enhanced by pretreatment with diethylthiocarbamate. *Eur J Pharmacol* 119:127-128.
- Coyle JT, Puttfarcken P (1993) Oxidative stress, glutamate, and neurodegenerative disorders. *Science* 262:689-695.
- Crowne D, Marlowe D (1960) A new scale of social desirability independent of psychopathology. *J Consult Psychol* 24:1397-1403.
- Cummings JL (1992) Depression and Parkinson's disease: A review. *Am J Psychiatry* 149:443-454.
- Derogatis LR (1975) *Symptom Checklist-90* (revised). Towson, MD: Clinical Psychometric Research, Inc.
- Doty RL, Shuman P, Applebaum SL, Giberson R, Sikorski L, Rosenberg L (1984) Smell identification ability: Changes with age. *Science* 226:1441-1443.
- Doty RL, Stern MB, Pfeiffer C, Gollomp SM, Hurtig HI (1992) Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 55:138-142.
- Duvoisin RC, Eldridge R, Williams A, Nutt J, Calne D (1981) Twin study of Parkinson disease. *Neurology* 31:77-80.
- Gilbert ME (1988) The NMDA antagonist, MK-801, suppresses limbic kindling and kindled seizures. *Brain Res* 463:90-99.
- Gilbert ME (1992) Neurotoxicants and limbic kindling. In RL Isaacson, KF Jensen (Eds), *The vulnerable brain and environmental risks: Vol 1. Malnutrition and hazard assessment* (pp. 173-192). New York: Plenum.
- Golbe LI, Langston JW (1993) The etiology of Parkinson's disease: New directions for research. In J Jankovic, E Tolosa (Eds), *Parkinson's disease and movement disorders* (2nd ed, pp. 93-101). Baltimore: Williams & Wilkins.
- Heafield MT, Fearn S, Steventon GB, Waring RH, Williams AC, Sturman SG (1990) Plasma cysteine and sulphate levels in patients with motor neurone, Parkinson's, and Alzheimer's disease. *Neurosci Lett* 110:216-220.
- Heikkila RE, Nicklas WJ, Vyas I, Duvoisin RC (1985) Dopaminergic toxicity of rotenone and the 1-methyl-4-phenylpyridinium ion after their stereotaxic administration to rats: Implication for the mechanism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity. *Neurosci Lett* 62:389-394.
- Herbener ES, Kagan J, Cohen M (1989) Shyness and olfactory threshold. *Pers Individ Diff* 10:1159-1163.
- Hirshfeld DR, Rosenbaum JF, Biederman J, Bolduc EA, Faraone SV, Snidman N, Reznick JS, Kagan J (1992) Stable behavioral inhibition and its association with anxiety disorder. *J Am Acad Child Adolesc Psychiatry* 31:103-111.
- Hooks MS, Jones GH, Neull DB, Justice JB (1992) Individual differ-

- ences in amphetamine sensitization: Dose-dependent effects. *Pharmacol Biochem Behav* 41:203-210.
- Iversen L, Foster AC, Hill RG, Iversen SD, Kemp JA, Leeson PD, Rupniak NMJ, Saywell K, Tricklebank MD, Williams BJ (1992) Neurotoxin-related research: From the laboratory to the clinic. *Ann NY Acad Sci* 648:207-218.
- Jamner L, Schwartz GE, Leigh H (1988) The relationship between repressive and defensive coping styles and monocyte, eosinophil, and serum glucose levels: Support for the opioid peptide hypothesis of repression. *Psychosom Med* 50:567-575.
- Jamner LD, Shapiro D, Goldstein IB, Hug R (1991) Ambulatory blood pressure and heart rate in paramedics: Effects of cynical hostility and defensiveness. *Psychosom Med* 53:393-406.
- Kagan J (1992) Behavior, biology, and the meanings of temperamental constructs. *Pediatrics* 90(Suppl):510-513.
- Kagan J, Reznick JS, Snidman N (1987) The physiology and psychology of behavioral inhibition in children. *Child Dev* 58:1459-1473.
- Kagan J, Reznick JS, Snidman N (1988) Biological bases of childhood shyness. *Science* 240:167-171.
- Kagan J, Snidman N, Julia-Sellers M, Johnson MO (1991) Temperament and allergic symptoms. *Psychosom Med* 53:332-340.
- Kalivas PW (1993) Neurotransmitter regulation of dopaminergic neurons in ventral tegmental area. *Brain Res Brain Res Rev* 18:75-113.
- Keller RW, Masonneuve IM, Carlson JN, Glick SD (1992) Within subject sensitization of striatal dopamine release after a single injection of cocaine: An in vivo microdialysis study. *Synapse* 11:28-34.
- Keller RW, Stricker EM, Zigmond MJ (1983) Environmental stimuli but not homeostatic challenges produce apparent increases in dopaminergic activity in the striatum: An analysis by in vivo voltammetry. *Brain Res* 279:159-170.
- Koller W, Vetere-Overfield B, Gray C, Alexander C, Chin T, Dolezal J, Hassanein R, Tanner C (1990) Environmental risk factors in Parkinson's disease. *Neurology* 40:1218-1221.
- Lane RD, Merikangas KR, Schwartz GE, Huang SS, Prusoff BA (1990) Inverse relationship between defensiveness and lifetime prevalence of psychiatric disorder. *Am J Psychiatry* 147:573-578.
- Mansour A, Doyle R, Katz R, Valenstein ES (1981) Long-lasting changes in behavior and morphine sensitivity following amygdaloid kindling in mice. *Physiol Behav* 27:1117-1120.
- Morrow LA, Ryan CM, Hodgson MJ, Robin N (1990) Alterations in cognitive and psychological functioning after organic solvent exposure. *J Occup Med* 32:444-450.
- Morrow LA, Ryan CM, Hodgson MJ, Robin N (1991) Risk factors associated with persistence of neuropsychological deficits in persons with organic solvent exposure. *J Nerv Ment Dis* 179:540-545.
- Mutti A, Franchini I (1987) Toxicity of metabolites to dopaminergic systems and the behavioral effects of organic solvents. *Br J Ind Med* 44:721-723.
- Olney JW, Zorumski C, Price MT, Labruyere J (1990) L-Cysteine, a bicarbonate-sensitive endogenous excitotoxin. *Science* 248:596-599.
- Parkinson's Study Group (1993) Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 328:176-183.
- Paulson GW, Dadmehr N (1991) Is there a premorbid personality typical for Parkinson's disease? *Neurology* 41(Suppl 2):73-76.
- Pearlin LI, Schooler C (1978) The structure of coping. *J Health Soc Behav* 19:2-21.
- Pezzoli G, Ricciardi S, Masotto C, Mariani CB, Carezzi A (1990) n-Hexane induces Parkinsonism in rodents. *Brain Res* 531:355-357.
- Poewe W, Gerstenbrand F, Ransmayr G, Plorer S (1983) Premorbid personality of Parkinson patients. *J Neural Trans Suppl* 19:215-224.
- Pollock M, Hornabrook RW (1966) The prevalence, natural history, and dementia of Parkinson's disease. *Brain* 89:429-448.
- Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 149:999-1010.
- Rajput AH, Offord KP, Beard M, Kurland LT (1987) A case-control study of smoking habits, dementia, and other illnesses in idiopathic Parkinson's disease. *Neurology* 37:226-232.
- Rajput AH, Rozdilsky B, Rajput A (1993) Alzheimer's disease and idiopathic Parkinson's disease coexistence. *J Geriatr Psychiatry Neurol* 6:170-176.
- Reznick JS, Hegeman IM, Kaufman ER, Woods SW, Jacobs M (1992) Retrospective and concurrent self-report of behavioral inhibition and their relation to adult mental health. *Dev Psychopathol* 4:301-321.
- Riklan M, Weiner H, Diller L (1959) Somato-psychologic studies in Parkinson's disease 1. An investigation into the relationship of certain disease factors to psychological functions. *J Nerv Ment Dis* 129:263-272.
- Robinson TE, Becker JB (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. *Brain Res Rev* 11:157-198.
- Robinson TE, Becker JB, Presty SK (1982) Long-term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: Sex differences. *Brain Res* 253:231-241.
- Rosenbaum JF, Biederman J, Bolduc EA, Hirshfeld DR, Faraone SV, Kagan J (1992) Comorbidity of parental anxiety disorders as risk for childhood-onset anxiety in inhibited children. *Am J Psychiatry* 149:475-481.
- Rosenbaum JF, Biederman J, Gersten M, Hirshfeld DR, Meminger SR, Herman JB, Kagan J, Reznick JS, Snidman N (1988) Behavioral inhibition in children of parents with panic disorder and agoraphobia. *Arch Gen Psychiatry* 45:463-470.
- Ryan CM, Morrow LA, Hodgson M (1988) Cacosmia and neurobehavioral dysfunction associated with occupational exposure to mixtures of organic solvents. *Am J Psychiatry* 145:1442-1445.
- Sapolsky RM (1992) *Stress, the aging brain, and the mechanisms of neuron death*. Cambridge, MA: MIT Press.
- Sawle GV, Wroe SJ, Lees AJ, Brooks DJ, Frackowiak RS (1992) The identification of presymptomatic Parkinsonism: Clinical and [¹⁸F]dopa positron emission tomography studies in an Irish kindred. *Ann Neurol* 32:609-617.
- Seegal RF, Shain W (1992) Neurotoxicity of polychlorinated biphenyls. The role of ortho-substituted congeners in altering neurochemical function. In RL Isaacson, KF Jensen (Eds), *The vulnerable brain and environmental risks: Vol 2. Toxins in food* (pp. 169-195). New York: Plenum.
- Semchuk KM, Love EJ, Lee RG (1992) Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology* 42:1328-1335.
- Snyder-Keller AM (1991) Striatal c-fos induction by drugs and stress in neonatally dopamine-depleted rats given nigral transplants: Importance of NMDA activation and relevance to sensitization phenomena. *Exp Neurol* 113:155-165.
- Steventon GB, Heafield MTE, Waring RH, Williams AC (1989) Xenobiotic metabolism in Parkinson's disease. *Neurology* 39:883-887.
- Tetrad JW, Langston JW (1989) The effect of deprenyl on the natural history of Parkinson's disease. *Science* 245:519-522.
- Todes CJ, Lees AJ (1985) The premorbid personality of patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 48:97-100.
- Turski L, Bressler K, Rettig PA, Loschmann A, Wachtel H (1991) Protection of substantia nigra from MPP⁺ neurotoxicity by N-methyl-D-aspartate antagonists. *Nature* 349:414-418.
- Wallace LA (1991) Volatile organic compounds. In JM Samet, JD Spengler (Eds), *Indoor air pollution. A health perspective* (pp. 252-272). Baltimore: Johns Hopkins University Press.
- Ward CD, Hess WA, Calne DB (1983) Olfactory impairment in Parkinson's disease. *Neurology* 33:943-946.
- Warrenburg S, Levine J, Schwartz GE, Fontana AF, Kerns RD, Delaney R, Mattson R (1989) Defensive coping and blood pressure reactivity in medical patients. *J Behav Med* 12:407-424.
- Weinberger DA (1990) The construct validity of the repressive coping style. In JL Singer (Ed), *Repression and dissociation: Implications for personality theory, psychopathology, and health* (pp. 337-386). Chicago: University of Chicago.
- Weinberger DA, Schwartz GE, Davidson R (1979) Low anxious, high anxious, and repressive coping styles: Psychometric patterns and behavioral and physiological responses to stress. *J Abnorm Psychol* 88:369-380.