Published in final edited form as:

Brain Imaging Behav. 2013 June ; 7(2): 163–176. doi:10.1007/s11682-012-9210-3.

Volunteerism and Self-Selection Bias in Human Positron Emission Tomography Neuroimaging Research

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Abstract

Scientists have known for decades that persons who volunteer for behavioral research may be different from those who decline participation and that characteristics differentiating volunteers from non-volunteers may vary depending on the nature of the research. There is evidence that volunteer self-selection can impact representativeness of samples in studies involving physically or psychologically stressful procedures, such as electric shocks, sensory isolation, or drug effects. However, the degree to which self-selection influences sample characteristics in "stressful" studies involving positron emission tomography (PET) has not been evaluated. Since estimation of population parameters, robustness of findings, and validity of inferred relationships can all be impacted by volunteer bias, it is important to determine if self-selection may act as an unrecognized confound in such studies. In the present investigation, we obtained baseline data on 114 M, F subjects who participated in a study involving completion of several self-report questionnaires and behavioral performance tasks. Participants were later given the opportunity to enroll in an [11C]raclopride PET study involving intravenous amphetamine (AMPH) administration. Demographic characteristics, personality traits, and task performance of subjects who consented to the latter study were compared with those who declined participation. Findings showed that the principal personality trait that distinguished the two groups was sensation-seeking; volunteers scored significantly higher on this dimension than non-volunteers. Males were more likely to volunteer than females. However, results of mediation analysis suggested that the relationship between gender and volunteer status was mediated by greater sensation-seeking traits in the males. Implications of these findings are discussed.

Keywords

Positron emission tomography (PET); Human; Volunteerism; Personality; Sensation-Seeking; Gender

1. Introduction

Over the past decade, research on the etiology of psychopathological conditions, such as bipolar disorder, obsessive-compulsive disorder, substance use disorders and schizophrenia, has been revolutionized by advancements in functional neuroimaging methods, which now make it possible to study dynamic relationships between the neurobiological and

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psychopathological manifestations of these disorders in humans. This clinical research has been complemented by concurrent use of functional neuroimaging technology to provide new insights into brain substrates/systems that contribute to normal variation in cognition, mood, personality, and behavior in healthy humans. Ultimately, better understanding of the interplay between such normal and abnormal processes may facilitate early identification of at-risk individuals, lead to better targeting of treatment interventions, and further the development of clinically relevant biomarkers of treatment response in patients who suffer from one or more of these debilitating neuropsychiatric conditions.

Subjects in positron emission tomography (PET) neuroimaging studies generally consist of 1) healthy adults who are presumed to have a reasonably normal distribution of scores on the characteristics of interest (e.g., novelty-seeking traits) or 2) clinical populations (e.g. cocaine abusers or schizophrenics) who are being compared to healthy controls on some measure of brain function. Typically, the large number of technological, methodological, and ethical considerations involved in these kinds of studies puts somewhat rigid restrictions on eligibility requirements. In most PET studies, research participants must be in good physical health, must not be using psychotropic medications, and must be able to commit the time involved in completing the procedures. Although the limitations in generalizability of findings that result from these restrictions are widely acknowledged by investigators, there is nevertheless a tacit assumption that samples are otherwise reasonably representative of the populations of interest. An important consideration that has rarely been addressed in this body of research is the potential for nonrepresentative samples and misinterpretation of findings secondary to self-selection of volunteers.

Scientists have known for decades that persons who volunteer for behavioral research may be different than those who do not. In 1975, Rosenthal and Rosnow published an extensive review of the literature which suggested that, in general, volunteers tend to be female, better educated, higher social class, more intelligent, more sociable, more unconventional, less authoritarian, more arousal seeking, and more approval-seeking than non-volunteers. Moreover, the evidence suggested that characteristics that differentiate volunteers from non-volunteers may vary as a function of the type of tasks involved in the study. Notably, males are more likely than females to volunteer for studies in which the procedures are physically or psychologically stressful or unconventional (e.g., electric shocks, high temperatures, fatigue, or sensory isolation) or in which sexual behavior or drug effects are being investigated. Arousal-seeking characteristics are also greater among persons who volunteer for more stressful studies.

Samples in more recent studies designed to evaluate personality characteristics of individuals who volunteer for “stressful” research procedures have been mostly male. Taken together, findings from these studies indicate that volunteers for Phase 1 trials (Almeida et al. 2008; Ball et al. 1993; Berto et al. 1996), pharmacological research (Donny et al. 2003; Pieters et al. 1992; Zuckerman 1979), potentially painful procedures (Gustavsson et al. 1997), hazardous combat simulation (Jobe et al. 1983), and human sexuality research (Bogaert 1996) are less neurotic, more extroverted, and have higher sensation-seeking and risk-taking traits when compared to non-volunteers or normative samples. Some (Almeida et al. 2008; Gustavsson et al. 1997; Skinner 1982), but not all studies (Pieters et al. 1992) have reported greater trait impulsivity in volunteers; findings related to psychoticism have also been mixed (Ball et al. 1993; Gustavsson et al. 1997).

Since PET neuroimaging research typically involves “stressful” procedures, such as radiation exposure, intravenous access, arterial lines, and/or drug administration, it is reasonable to speculate that a potential for self-selection bias exists in these studies. Self-selection could result in over- or under-estimation of population parameters and limited generalizability of findings in such research. Perhaps even more bothersome and more insidious is the potential for Type I and Type II error leading to questionable and even inaccurate conclusions. For example, there is considerable evidence that dopamine (DA) function plays a role in both sensation-seeking behavior and drug abuse. Over-representation of persons with high sensation-seeking traits in studies on drug abuse could hypothetically lead to reduced ability to detect statistical differences in DA function between drug abusers and normal controls if both groups were high in sensation-seeking traits (Type II error). There is also evidence that pharmacodynamic and pharmacokinetic effects of both psychoactive drugs and placebos can be influenced by personality traits such as extraversion and neuroticism (Kelley et al. 2009; Kelly et al. 2006; Meyer 2001; Ralevski et al. 2010; Smillie and Gokcen 2010; Tishler et al. 2005). Thus, sample homogeneity on such characteristics could function as an unrecognized confound with a marked influence on experimental outcomes, potentially leading to causal inferences that would not hold up in a more representative sample.

To our knowledge, no empirical research has been conducted to evaluate the degree to which volunteers for PET research represent a self-selected population. An obvious problem in trying to make comparisons between volunteers and non-volunteers is that data is often not available from non-volunteers. One strategy that has been used to circumvent this problem in other kinds of research is to use a two-phase recruitment, which involves soliciting volunteers for higher-risk studies among persons who have previously volunteered and provided data for less “stressful” types of research (Rosenthal and Rosnow 1975). In the current study, we used this method to determine whether demographic or personality characteristics of PET volunteers differ from those who decline participation. Individuals who initially volunteered for a study involving self-report questionnaires and computerized behavioral tasks were later given the opportunity to participate in a PET study involving [11C]raclopride and intravenous amphetamine (AMPH) administration. Baseline characteristics of individuals who provided informed consent for the latter study were compared with those who declined participation. We hypothesized that males would be more likely to volunteer than females and that greater arousal-seeking characteristics would be observed in volunteers as compared to non-volunteers.

2. Material and methods

2.1. Participants

One-hundred and fourteen healthy male (n=56) and female (n=58) participants, ages 18 to 29 years, were recruited from the Baltimore metropolitan area by posted flyers, newspapers, and internet advertisements for participation in Phase 1 of a two-phase study designed to examine relationships among impulsive personality traits, chronic stress, brain function, and risks for drug abuse. The text of the ads indicated that the study involved completion of an in-person interview, self-report questionnaires and computer tasks. The research was approved and overseen by the University of Maryland and the Johns Hopkins Medicine Institutional Review Boards.

Respondents who appeared to qualify on the basis of a brief telephone screen were invited to our research offices at the University of Maryland to provide informed consent. Psychiatric diagnostic screening was conducted using the Structured Clinical Interview for DSM Disorders (SCID-I/NP; First et al. 2002). Alcohol and drug use patterns were further evaluated by 90-day timeline follow back (Sobell and Sobell 1992; 1995). Additional screening measures included the Beck Depression Inventory (BDI; Beck et al. 1996), Shipley Institute of Living Scale-2 (Shipley et al. 2009), Fagerstrom Test for Nicotine Dependence (Heatherton et al. 1991), a brief medical history questionnaire, alcohol breathalyzer test, urine toxicology, and urine pregnancy test (women).

Exclusion criteria included history of a DSM-IV psychiatric Axis I disorder (American Psychiatric Association 2000); currently in need of psychiatric treatment; illicit drug use during the past 30 days (self-report or urine drug screen); lifetime stimulant use; nicotine dependence or smokes more than 10 cigarettes per week; heavy alcohol consumption (i.e., > 7 drinks/week for women or > 14 drinks/week for men); current use of a hormonal measure of birth control or hormone replacement therapy; pregnant or lactating; serious medical conditions; treatment in the last 12 months with antidepressants, neuroleptics, sedative/ hypnotics, appetite suppressants, opiates, antihypertensives, or dopamine medications; claustrophobia or fear of needles; BMI < 20 or > 31; and less than a 5th grade reading level.

2.2. General Procedures

Following the intake screening interview and completion of self-report questionnaires, eligible participants took part in a behavioral performance session that included administration of a battery of four computerized measures of impulsivity and one measure of risk-taking behavior (see below). The performance session was generally conducted on the same day as the initial assessment, but could be scheduled for another day if needed.

Subjects who completed the behavioral performance computer session were informed before they left our research office that there was another part of the study for which they may now be eligible. They were given a brief verbal, scripted overview of the Phase 2 procedures. If they indicated that they might be interested in participation, they were given the opportunity to provide informed consent. Procedures described in the Phase 2 consent form included a structural magnetic resonance imaging (MRI) scan and two consecutive 90-minute PET scans with [11C]raclopride and intravenous amphetamine injection. Participants who enrolled in Phase 2 were required to undergo further medical evaluation to confirm eligibility, including a history and physical examination, standard laboratory tests, and electrocardiogram (ECG).

Differences in demographic characteristics and personality traits of the PET study volunteers and non-volunteers were evaluated based on their responses to the self-report questionnaires and behavioral performance tasks administered during Phase 1. All subjects were compensated for participation.

2.3. Self-Report Measures

Higher- and lower-order dimensions of the ‘Big Five’ model of personality were examined at the initial intake session using the NEO Personality Inventory (NEO-PI-R; Costa and McCrae 1992). A more targeted profile of impulsive personality and related traits was obtained with the Barratt Impulsiveness Scale (BIS-11; Patton et al. 1995), Sensation-Seeking Scale (SSS; Zuckerman et al. 1978), and Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al. 2001).

2.3.1. Revised NEO Personality Inventory (NEO-PI-R)—The NEO is a 240-item questionnaire that measures five major personality factors: Neuroticism (N), Extraversion (E), Openness to Experience (O), Agreeableness (A), and Conscientiousness (C). The major factors are each differentiated into six subscales or “facets” that represent groups of intercorrelated traits. Individuals high in Neuroticism have a susceptibility to psychological distress and disruptive emotions; (facets: Anxiety, Anger Hostility, Depression, Self-Consciousness, Impulsiveness, and Vulnerability). Extroverts tend to be social, assertive, energetic, and like excitement (facets: Warmth, Gregariousness, Assertiveness, Activity, Excitement-Seeking, and Positive Emotions). Openness to Experience is associated with active imagination, attention to inner feelings, willingness to entertain novel ideas, and intellectual curiosity (facets: Fantasy, Aesthetics, Feelings, Actions, Ideas, and Values). The

Agreeable person is fundamentally altruistic and sympathetic to others (Trust, Straightforwardism, Altruism, Compliance, Modesty, and Tender mindedness). The Conscientious person is purposeful, determined, scrupulous, and reliable (facets: Competence, Order, Dutifulness, Achievement Striving, Self-Discipline, and Deliberation). Items are answered on a 5-point Likert scale from "strongly agree" to "strongly disagree". Standardized *T*- scores <45 are considered in the low range, 45–55 are average, and >55 are high.

2.3.2. Barratt Impulsiveness Scale (BIS-11)—The BIS-11 is a 30-item self-report questionnaire that measures three different dimensions of impulsivity: motor (acting without forethought), attentional (tendency to make quick, nonreflective decisions), and nonplanning (failure to prepare for future events). Items are answered on a 4-point Likert-like scale from "rarely/never" to "almost always/always". Three subscale scores and a total score can be calculated. The BIS has been validated in several different populations. Internal consistency estimates in groups of college undergraduates, patients with substance use disorders, psychiatric patients, and prison inmates have ranged from 0.79–0.83.

2.3.3. Sensation Seeking Scale - Form V (SSS)—The SSS is a 40-item questionnaire that measures individual differences in optimal levels of stimulation and arousal on four subscales: Thrill and Adventure Seeking (TAS); Experience Seeking (ES); Disinhibition (DIS); and Boredom Susceptibility (BS). TAS describes the desire to engage in physically dangerous activities. ES is related to the desire to experience new things through the mind and senses. DIS is associated with the need to disinhibit behavior socially (e.g., by partying). BS indicates an aversion to any kind of repetitive activity, including work and people. Each subscale consists of ten items. Subscale scores can range from 0–10; total score can range from 0–40. Reliability, construct, and convergent validity have been well established. Men have been reported to score higher on this measure than women over the lifetime (Zuckerman et al. 1978).

2.3.4. Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)—The SPSRQ is a 48-item scale designed to assess individual differences in two components of Gray's (1981) model of personality which describes two motivational systems, the Behavioral Inhibition System (BIS) and the Behavioral Activation System (BAS). These systems are proposed to control aversive and appetitive behaviors, respectively. The Sensitivity to Punishment (SP) scale measures 1) behavioral inhibition in situations involving adverse consequences or novelty and 2) worry produced by threat of punishment or failure. The Sensitivity to Reward (SR) scale contains items that describe situations where a person could carry out certain actions to obtain rewards, such as money, sex partners, social events, or power. Construct validity is supported by expected relationships with other individual difference measures. Test-retest reliabilities were performed on the SP and SR at three months (r=0.89 and 0.87), one year (r=0.74 and 0.69), and three years (r=0.57 and 0.61), respectively.

2.4. Behavioral Performance Measures

A battery of five computerized measures of impulsivity and risk-taking behavior were administered in semi-randomized order (the IMT/DMT and GoStop were never presented consecutively due to task demands). The session began at approximately 1 pm for all subjects and lasted a total of approximately 2½ hours. Standardized instructions were given prior to each of the tasks. Five-minute breaks were given between tasks, which each varied in length from approximately 6 minutes to 20 minutes. To discourage indiscriminate responding, participants were told that a portion of their earnings for the day would depend on the points they earned on the tasks. In reality, all participants were paid the maximum possible earnings.

2.4.1. Immediate and Delayed Memory Tasks (IMT/DMT)—The IMT/DMT are modified Continuous Performance Tasks used to assess individual differences in premature responding (Dougherty and Marsh 2003). The two tasks are administered consecutively (i.e., IMT followed by DMT). The IMT was designed to measure brief attentional capacity; the DMT was designed to measure a participant's ability to retain a stimulus in memory for longer periods of time. For the IMT, a series of 5-digit numbers (e.g. 59312) appear on the monitor. Participants are instructed to respond by clicking on the computer mouse button when the number is identical to the one that immediately preceded it. Numbers are displayed for 0.5 sec. and separated by a 0.5 sec. blackout period. Any response made while a target stimulus appears on the monitor before the next stimulus appears is recorded as a correct hit. Catch stimuli are numbers that closely resemble the numbers immediately preceding them. Responses to these stimuli are called commission errors. A filler stimulus is a random 5-digit number that appears whenever target or catch stimuli are not scheduled to appear. Points are earned for correct hits and subtracted for errors. The main difference between the IMT and DMT is that stimuli are separated by 3 presentations of the number 12345 in the DMT. Participants are told to ignore the 12345 stimuli and compare only stimuli that are not 12345. The IMT and DMT ratios (i.e., proportion of commission errors to correct detections) are the primary dependent measures. Considerable variability in scores has been observed even in normal controls (Dougherty et al. 2003b). Acceptable reliability has been reported both within and across testing periods (Mathias et al. 2002).

2.4.2. GoStop Impulsivity Paradigm—The GoStop is a stop-signal task that measures response inhibition (i.e., the capacity to inhibit an already initiated response; Dougherty 2003). This task involves rapid presentation of a series of 5-digit numbers, each displayed for 500 ms with a 1500 ms inter-stimulus interval. Subjects are instructed that they may earn points by responding with a mouse click if a number matches the one that immediately preceded it. Half of the numbers are target trials (matching stimuli) and half are filler trials (nonmatching stimuli). Participants are told that they must respond to a number while it is still on the screen to earn points. However, they must withhold responding if a number changes from black to red (stop signal) or they will lose points. The matching number changes from black to red in half of the target trials at intervals of 50, 150, 250, and 350 ms after stimulus onset. Impulsivity is defined as a failure to inhibit responding following the "stop" signal. The primary dependent variable is the GoStop ratio (i.e., proportion of response inhibition failures relative to the number of responses on go trials). Data from the 150 ms stop trials have been reported to provide the best discrimination among groups (Marsh et al. 2002).

2.4.3. Two Choice Impulsivity Paradigm (TCIP)—The TCIP is a forced-choice, reward-directed procedure for assessing tolerance for delayed reward (Dougherty 2003). Subjects experience a series of trials in which they must press a mouse button to select one of two shapes appearing on a computer monitor. Each shape-choice is associated with a different delay-reward contingency. Choosing one of the shapes results in a small reward (e.g., 5 points) after 5 sec.; choosing the other shape results in a larger reward (e.g., 15 points) after 15 sec. More impulsive responding is defined by a greater number of smaller-sooner reward choices or by a lower number of consecutive larger-later reward choices. The paradigm has been validated across a range of populations, including adolescents (Dougherty et al. 2003a), violent and nonviolent parolees (Cherek et al. 1997), and cocaine abusers (Moeller et al. 2002).

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2.4.4. Single Key Impulsivity Paradigm (SKIP)—The SKIP is a free-operant operant proecedure that measures tolerance for delayed reward (Dougherty 2003). Participants are instructed that they may earn points by clicking a computer mouse button in a session that will last 20 minutes. They are told that nothing in the task will tell them when to press the button, but the longer they wait before pressing the button, the more points each press will be worth. Each response adds earnings in direct proportion to the interval since the previous response, 1 cent for every 2 seconds since the last response. Two counters are displayed on the computer screen - one for the cumulative total of points earned during the session and the other for the number of points earned on the most recent response. Subjects are not given specific information about the delay contingency, although they may infer this from the money counter at the bottom of the screen that provides feedback for each response. Primary dependent measures are the total number of responses and the longest delay between responses.

2.4.5. Iowa Gambling Task (IGT)—The Iowa Gambling Task is a decision-making or risk-taking paradigm designed to simulate real-life decisions in terms of uncertainty, reward, and punishment (Bechara et al. 1994). Subjects choose between decks of cards that yield high immediate gains but also are associated with risk of high losses, and decks that yield low immediate gains and risk of smaller losses. Subjects are instructed to win as much money as possible by picking one card at a time from each of 4 decks (A, B, C, and D) until the computer instructs them to stop. Each subject is required to make 100 choices. The decks differ along two dimensions: Every card from decks A and B yields a gain of $100 in play money and every card from decks C and D yields a gain of $50. A certain number of cards in each of the 4 decks also carry a penalty such that the accumulated penalties are larger than the accumulated gains in decks A/B (disadvantageous) and are smaller than the accumulated gains in decks C/D (advantageous). The optimal strategy is to minimize the overall loss by avoiding the short-term appeal of decks A/B in favor of the slower, but ultimately positive gain of decks C/D. The net score is the total number of selections from decks A and B (disadvantageous) subtracted from the total number of selections from decks C and D (advantageous).

2.5. Statistical Analyses

Independent samples t-tests were used to compare scores on self-report personality questionnaires and behavioral performance measures between participants who volunteered vs. those who did not volunteer for the Phase 2 PET imaging procedures. Individual comparisons included NEO factor and subscale scores, total and subscale scores for each of the other self-report measures, and primary outcome measures on the behavioral tasks. Group differences in demographic indicators of age, educational level, and drinking history were also examined with independent samples t-tests. Chi-square analyses were used to evaluate differences in gender, race, and employment status. Pearson product-moment correlations were conducted to evaluate relationships among personality variables that showed statistical significance in the t-tests. Gender differences in personality traits were examined using linear regression analyses. A two-tailed alpha for significance was set at 0.05.

To evaluate the relative contributions of the predictor variables, a logistic regression analysis was then conducted using volunteer status as the dependent variable and the variables that showed significant relationships with volunteerism in the bivariate analyses as covariates. Based on associations observed in the logistic regression analysis, we also tested whether sensation seeking may moderate or mediate the association between gender and volunteerism. A moderator variable specifies under what conditions a predictor variable influences the dependent variable. Moderation effects are evaluated by testing the interaction between the predictor and the moderator variable (Baron & Kenny, 1986; Holmbeck, 1997; Kim et al., 2001). In this study, interactions between sensation seeking and gender were tested in the multiple logistic regression model. A significant interaction term indicated moderation effects. A mediator represents an intervening variable (often an attribute or an intrinsic characteristic of individuals) which falls in the causal pathway between the predictor variable and the dependent variable and which helps to explain the mechanism or process that underlies an observed relationship between the predictor and dependent variables (Aldwin, 1994; Holmbeck, 1997; Kim et al., 2001; Lindley & Walker, 1993; Peyrot, 1996). The mediation effect involved examination of four associations (Baron and Kenny 1986): (1) gender and volunteerism (*c* path); (2) gender and sensation seeking (*a* path); (3) sensation seeking and volunteerism while controlling for gender (*b* path); and (4) gender and volunteerism with sensation seeking included in the model (c' path). The amount of mediation (indirect effect) was the product of the coefficients for path a and path b (i.e., *a**b*). The significance of the mediation effect (a*b) was tested by the Bootstrapping method, which does not require the normality assumption of the outcome variable to be met and is effectively utilized with relatively small sample sizes (MacKinnon 2008; MacKinnon et al. 2002; Shrout and Bolger 2002).

Secondary analyses included the use of t-tests and Chi-square analyses to evaluate 1) whether scores on measures that were entered into the logistic regression model differed between Phase 2 volunteers who completed the PET scans and those who either withdrew from the study or were lost to follow up before completing the scans. Equality of standard deviations of SSS scores in volunteers vs. non-volunteers was evaluated with the *F*-Test. All analyses were performed using STATA11.0 (StataCorp 2009).

3. Results

3.1. Bivariate Analyses

Table 1 presents results of selected t-tests and Chi-square analyses conducted on demographic, self-report, and behavioral performance measures. Among the 114 Phase 1 volunteers, approximately 43% consented to participate in the Phase 2 PET neuroimaging procedures. Males were more likely to volunteer for the PET scans than females. Marginal differences were observed as a function of race/ethnicity, which seemed to be largely attributable to a lower rate of volunteerism among Asians than among any of the other groups. Minimal personality differences were found between PET volunteers and non-volunteers. Volunteers had higher total SSS scores ($p < 0.001$) and higher scores on all subscales of this measure ($p < 0.01$ in all cases) than non-volunteers. The only other significant differences that were observed in self-report personality traits were lower scores on the NEO Openness factor ($p = 0.004$), which seemed to be accounted for primarily by scores on the Values facet ($p = 0.042$), lower NEO Impulsiveness scores ($p = 0.03$), and higher NEO Competence scores ($p = 0.027$) in volunteers vs. non-volunteers. None of the behavioral performance measures significantly discriminated between the two groups. However, non-significant trends were observed for greater commission errors in the volunteer group on both the IMT and DMT.

Intercorrelations among the personality variables that demonstrated predictive relationships with volunteerism in the t-tests are presented in Table 2. Findings of separate individual regression analyses showed that males exhibited greater sensation-seeking traits than females on all subscales of the SSS ($p < 0.05$ in all cases). The mean total SSS score for males was 20.75 (SD = 5.6) and for females was 15.33 (SD = 6.5) ($R^2 = .167$, $F(1,113) = 22.46$, $p < 0.001$). No other statistically significant differences were found between men and women on the predictor variables.

3.2. Logistic Regression Analysis

High multicollinearity precluded the use of both the SSS total and subscale scores as covariates in the logistic regression model, hence only the total SSS was employed along with the five other variables that showed statistically significant associations with volunteerism in bivariate analyses. As shown in Table 3, the SSS total score remained a significant predictor after adjusting for the other covariates. One unit increase in SSS was related to 11% increase in the likelihood of participating in the PET neuroimaging procedures (adjusted OR=1.11, 95% CI: 1.03–1.20; p=0.008). In contrast, individuals with greater NEO Impulsiveness scores had a slightly lower likelihood of participating (adjusted OR=0.92, 95% CI: 0.86–0.99, p=0.016). After adjusting for the other covariates, the NEO Openness to Experience Factor was only marginally related to volunteerism. None of the other measures remained significant predictors.

3.3. Moderation/Mediation Analyses

No interaction was observed between sensation seeking and gender in the multiple logistic regression model (p=0.81), indicating that the relationship between sensation-seeking and volunteerism does not differ between males and females. Figure 1 shows the model assessing mediation effects of sensation-seeking on the association between gender and PET volunteerism. Findings showed that when sensation seeking was included in the model, the effect of gender on volunteerism was reduced by 81% (from $\beta=-0.862$, p=0.026 to $\beta=-0.164$, p=0.487). The product of coefficients showed that the indirect effect was significant (a*b=−0.372, CI:−0.642–−0.176, p=0.002), indicating that sensation seeking partially mediates the relationship between gender and volunteerism.

3.4. Secondary Analyses

Of the 49 participants who consented to the PET procedures, 20 (41%) actually completed the scans. Almost half of those who did not complete the study were excluded for reasons such as abnormal values on laboratory tests, which prohibited participation. The remainder either withdrew from the study or were lost to follow up. The most common reason given for withdrawal was lack of time. The average amount of time that elapsed between informed consent and scan completion was approximately 2 months. No differences were found between volunteers who completed vs. those who did not complete the PET scans on any of the variables that were entered into the logistic regression model (i.e., gender, Sensation-Seeking, Openness, Impulsiveness, Values, or Competence).

A statistically significant difference was found in the variance of SSS scores between volunteers and non-volunteers ($F(49,65) = 4.87$; $p = .004$), suggesting that the spread of scores was greater in the non-volunteers. The distributions of each of the two groups are displayed in Figure 2. When the number of subjects with scores in each tertile of the distribution was examined, findings showed that 53.85 % of non-volunteers had SSS scores in the lower tertile of the distribution (scores 1 – 14) as compared to only 12.24 % of volunteers. However, scores of the remainder of subjects within each of the two groups were reasonably balanced between the middle (scores 15 – 21) and upper (scores 22 – 31) tertiles.

4. Discussion/Conclusions

This study used a two-phase recruitment method to evaluate the degree to which individuals who volunteer for PET neuroimaging research represent a self-selected population. To date, little is known about personality traits or other individual characteristics that may affect experimental outcomes in such research. Subjects who completed a study involving self-report questionnaires and computerized behavioral tasks were later given the opportunity to volunteer for a PET study involving [11C]raclopride and intravenous amphetamine (AMPH) administration. Although minimal differences were found between individuals who volunteered for the PET study and those who declined to participate, one variable that clearly distinguished the two groups was sensation-seeking personality traits. These results are consistent with evidence showing that volunteers in other kinds of research involving stressful or risky procedures have greater sensation- or arousal-seeking characteristics than non-volunteers (Bogaert 1996; Gaither et al. 2003; Jobe et al. 1983; Rosenthal and Rosnow 1975; Thomas 1989). Males were more likely to volunteer for the PET scans than females, although effects of gender were no longer significant after being adjusted for sensation-seeking and other covariates in a logistic regression model. However, because males also exhibited higher sensation-seeking traits than females, we evaluated the possibility that the relationship between gender and volunteerism may be partially mediated by sensation-seeking. This hypothesis was supported by results of the mediation analysis, which indicated that the higher sensation-seeking traits partially explain why males are more likely to volunteer for “stressful” studies than females. Approximately 41% of the participants who initially volunteered for PET scans completed the procedures. No differences were found between scan completers and non-completers on any of the variables that were entered into the logistic regression model, including sensation-seeking traits.

The [11C]raclopride scans in the current study did not include the use of arterial lines. Thus, the most “painful” part of the procedures involved the insertion of two intravenous catheters, which is typically not considered highly aversive. This suggests that greater volunteerism among high sensation-seekers was related more to a need for excitement or novelty-seeking, than to a reduced sensitivity to negative experiences. Zuckerman and Kuhlman (2000) defined sensation-seeking as “the seeking of novel situations and the willingness to take risks for the sake of such stimulation” (p. 1015). Individual differences in this trait are determined by both genetic and environmental influences (Stoel et al. 2006), with heritability estimates ranging from 40% to 60% (Fulker et al. 1980; Hur and Bouchard 1997; Koopmans et al. 1995). In nonclinical samples, high sensation-seeking is associated with engaging in risky sports and vocations, criminal activities, drinking and drug use, reckless driving, gambling, and nonconforming attitudes (Franques et al. 2003; Jack and Ronan 1998; Loas et al. 2001; Zuckerman 1983; 1984). High sensation seeking has also been associated with clinical conditions, such as mania (Zuckerman and Neeb 1979), antisocial behavior (Vermeiren et al. 2002), and substance use disorders (Dom et al. 2006; Jardin et al. 2011; Pokhrel et al. 2010). Among alcohol and drug abusers, higher sensation seeking is linked to earlier age of onset of substance use (Brennan et al. 1986; Sargent et al. 2010; Wills et al. 1994), greater amount of use (Hittner and Swickert 2006; Martins et al. 2008), greater impairment (Ball et al. 1995; Hawkins et al. 1992), and worse treatment outcome (Staiger et al. 2007). Thus, there is considerable reason to believe that neurocognitive function and behaviors of self-selected samples of high sensation-seekers may not be representative of the general population.

Concern about the representativeness of volunteer samples is based on the need to minimize bias and error in statistical decision making and to maximize generality of research findings (Rosenthal and Rosnow 1975). Data from the current study have particular relevance for behavioral PET neuroimaging investigations that seek to examine 1) neurobiological underpinnings of sensation-seeking traits, 2) differences between healthy controls and patients with disorders in which externalizing behaviors are defining features, and 3) relationships between brain function and other variables that may interact with sensation-seeking. A restricted range of sensation-seeking scores could potentially result in a lack of power to detect the relationships of interest in these kinds of studies. There is also potential for overestimation or underestimation of population parameters when samples are nonrepresentative. One concern would be over-representation of high sensation-seekers in healthy control volunteers. Our findings showing that volunteers had higher mean SSS scores than non-volunteers suggest that if sensation-seeking covaries with the dependent variable, there is a possibility that volunteer bias could result in increased homogeneity and decreased ability to detect true population differences between groups of healthy controls and clinical patients. This may, in fact, be one factor that should be taken into consideration when interpreting negative results in such studies. Another problem concerns generalizability of findings. Observed relationships between brain function and behavior may not generalize to the population at large if sensation-seeking interacts with the behavior of interest and low sensation-seekers are under-represented in the sample. The nature of PET neuroimaging procedures, which often requires exclusion of patients with the most severe symptoms, may actually open the door for uncharacteristically low levels of sensation-seeking traits in the clinical samples, which would result in similar kinds of issues.

Mean SSS scores of PET study volunteers were significantly higher than those of non-volunteers (Table 1). Although the range of SSS scores was more restricted in PET volunteers than non-volunteers (Figure 2), examination of the distributions suggests that the group differences were primarily the result of a disparity in proportions in the lowest tertile of scores. Relatively few volunteers (12.24%) had scores lower than 15; whereas, over half of the non-volunteers (53.85%) fell into this category. The remainder of scores within each of the groups was nearly evenly distributed within the upper two tertiles of their respective distributions. The spread of scores suggests that volunteer bias may not have a *marked* influence on statistical power in correlational PET research when the relationships of interest vary along a continuum within the general population. Results of recent imaging studies that have examined whether brain dopamine (DA) function mediates individual differences in sensation-seeking traits tend to support this interpretation. Findings of these studies in healthy adults have shown negative associations between midbrain dopamine (DA) D_2 receptor availability and novelty-seeking (Zald et al. 2008), positive associations between amphetamine-induced DA release and novelty-seeking (Leyton et al. 2002), and an inverted-U-shaped correlation between striatal $DA_{2/3}$ receptor availability and sensation-seeking (Gjedde et al. 2010). In general, results support theoretical frameworks that have implicated DA systems in approach behaviors (Cloninger 1987; Depue and Collins 1999; Zuckerman and Kuhlman 2000). Although means and SDs on the personality scales have generally not been reported in these studies, visual examination of figures presented in the Gjedde report suggests that the distribution of SSS scores was negatively skewed (range approximately 8–32), but that there was a reasonably good spread of scores in the upper two-thirds of the distribution, which resembles the pattern observed in the present sample.

An interesting finding of the present study was that sensation-seeking partially mediated the relationship between gender and volunteerism. We found in bivariate analyses that males were more likely to volunteer for the PET study than females. However, the relationship between gender and volunteer status was no longer significant when all of the predictor variables were entered into a logistic regression model. These findings suggested that the predictive power of gender was either negated or mediated by another factor in the model (Christenfeld et al. 2004). Given that sensation-seeking traits were also found to be higher in males than in females in the bivariate analyses, we examined the possibility that the relationship between gender and volunteer status was mediated by sensation-seeking. To our knowledge, this research is the first to show that differences in sensation-seeking traits may account for a large part of the gender differences in rates of volunteerism for higher-risk studies. This finding is consistent with prior evidence that gender differences in impulsive sensation-seeking mediate differences in a range of risky behaviors (Zuckerman and Kuhlman 2000). The mediator model helps to explain *why* males are more likely to volunteer than females. However, since the findings showed partial, rather than full mediation, we conclude that other factors besides sensation-seeking may also play a role.

Interestingly, gender differences in brain DA function have been reported in the recent literature, including differences in nigrostriatal dopamine transporter (DAT) binding (Wong et al. 2012), ventral striatal $D_{2/3}$ receptor binding potential in response to unpredictable monetary reward (Martin-Soelch et al. 2011), $D_{2/3}$ receptor binding potential in the frontal cortex, temporal cortex, and thalamus (Kaasinen et al. 2001), as well as striatal DA release in response to amphetamine (Munro et al. 2006; Riccardi et al. 2006). These findings raise questions about whether differences in sensation-seeking behaviors between men and women are mediated by differences in DA function. Riccardi and colleagues (2006) examined this possibility, showing that left ventral striatal DA release following oral amphetamine was positively associated with sensation-seeking in males (n=7), but not in females (n=6), which suggested that regional DA function may mediate behavior differently in males vs. females. We found no interaction between gender and SSS scores in the logistic regression model, indicating that the relationship between sensation-seeking and volunteerism did not differ between males and females.

The only other personality variable that significantly differentiated volunteers from non-volunteers in the logistic regression model was NEO Impulsiveness. Curiously, PET volunteers scored lower on this dimension than non-volunteers, suggesting that they have less difficulty controlling cravings and urges. It is possible that individuals who are less inclined to give in to urges may be more focused on tasks at hand, such as participating in research, irrespective of the nature of the study. However, it is also possible and probably more likely that even though SSS scores were statistically different between volunteers and non-volunteers, they may not be meaningfully different. The NEO scores are standardized *T*-scores; our findings showed a difference of only 3.3 points between groups and means of both groups were in the low normal range. Intercorrelations among the self-report measures showed no relationship between sensation-seeking and NEO impulsivity, which is consistent with prior evidence that the two dimensions are conceptually distinct and have unique associations with externalizing behaviors and substance abuse (Castellanos-Ryan and Conrod 2011; Castellanos-Ryan et al. 2011; Cross et al. 2011; Dom et al. 2006; Ersche et al. 2010; Harden and Tucker-Drob 2011; Magid et al. 2007). Scores on the behavioral performance measures of impulsivity were not associated with volunteerism, with the exception of non-significant trends for greater commission errors on the IMT and DMT in volunteers as compared to non-volunteers. The latter finding may indicate that volunteers have greater tendencies for premature responding than non-volunteers.

One caveat of the current study is that our comparison group of non-volunteers may actually be at an intermediary level along a continuum of volunteerism. Although the non-volunteers declined to participate in the PET study, they did volunteer to participate in the study involving only interviews, questionnaires, and computer tasks. A limitation of our design was that it did not allow us to compare characteristics of PET volunteers with those of ‘true’ non-volunteers, but rather with those of persons who consented to participate only in less invasive research. If there is a gradient of volunteerism (which may or may not be the case), it is possible that our findings underestimate differences between PET volunteers and the ‘true’ non-volunteers who fall at the lower end of the gradient. Findings of the present study may not generalize to all types of PET neuroimaging research. For example, one could speculate that some individuals who declined to participate in the current PET study might volunteer for a PET study that did not include psychoactive drug administration. Additionally, It should be noted that the upper limit of SSS scores may have been somewhat truncated in our sample due to the need to exclude heavy drinkers and persons with an Axis I disorder, including nicotine dependence.

In summary, although artifacts related to volunteer bias may occur in any type of research, the influence of arousal-seeking characteristics has been reported to be a particular concern

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in studies involving exciting, demanding, or stressful procedures. Findings of the present study support and extend conclusions drawn about volunteerism from other kinds of biomedical research by showing that the type of individuals who may be drawn to volunteer for studies involving PET neuroimaging procedures are those with higher sensation-seeking traits. Although, the influence of self-selection on experimental outcomes may not be large in some cases, the potential for positive and negative bias related to arousal-seeking traits should be taken into consideration and addressed as indicated when recruiting subjects, conducting data analyses, and interpreting findings in many such studies. Distributions of scores should also be examined and descriptive statistics reported so that generalizability of findings can be evaluated and accurate conclusions drawn.

Acknowledgments

This work was supported by NIH grants R01 DA022433 (LMO) and M01 RR016500 (UMSOM GCRC). The authors are grateful to Mark Streer for his assistance with manuscript preparation.

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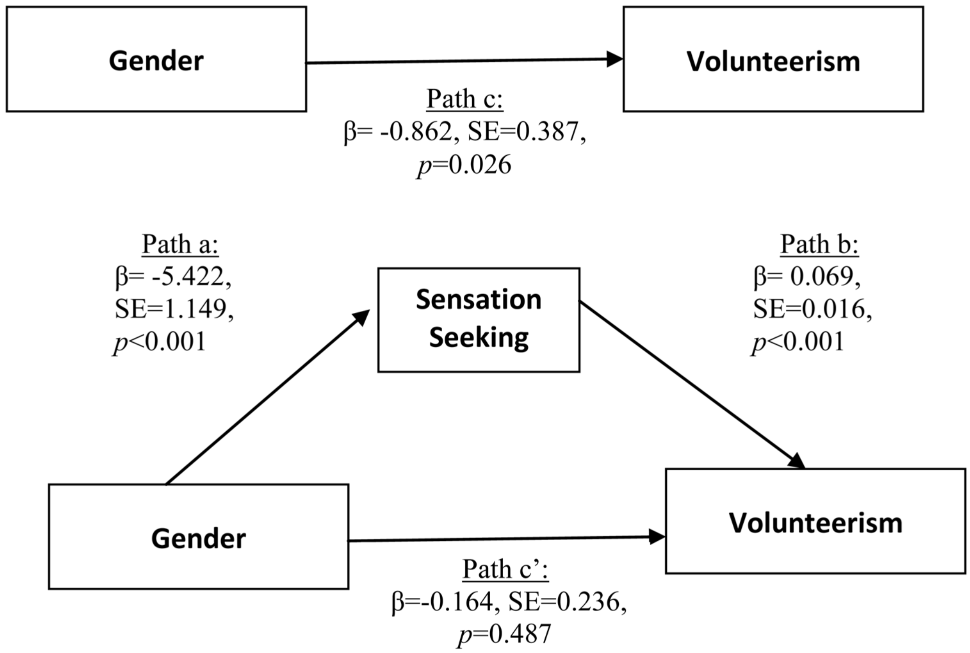

Figure 1.
Model depicting the direct and indirect effects of gender on PET volunteerism. Note: the indirect effect from gender to volunteerism through sensation-seeking was significant (a*b = −0.372, SE = 0.118, $p = 0.002$).

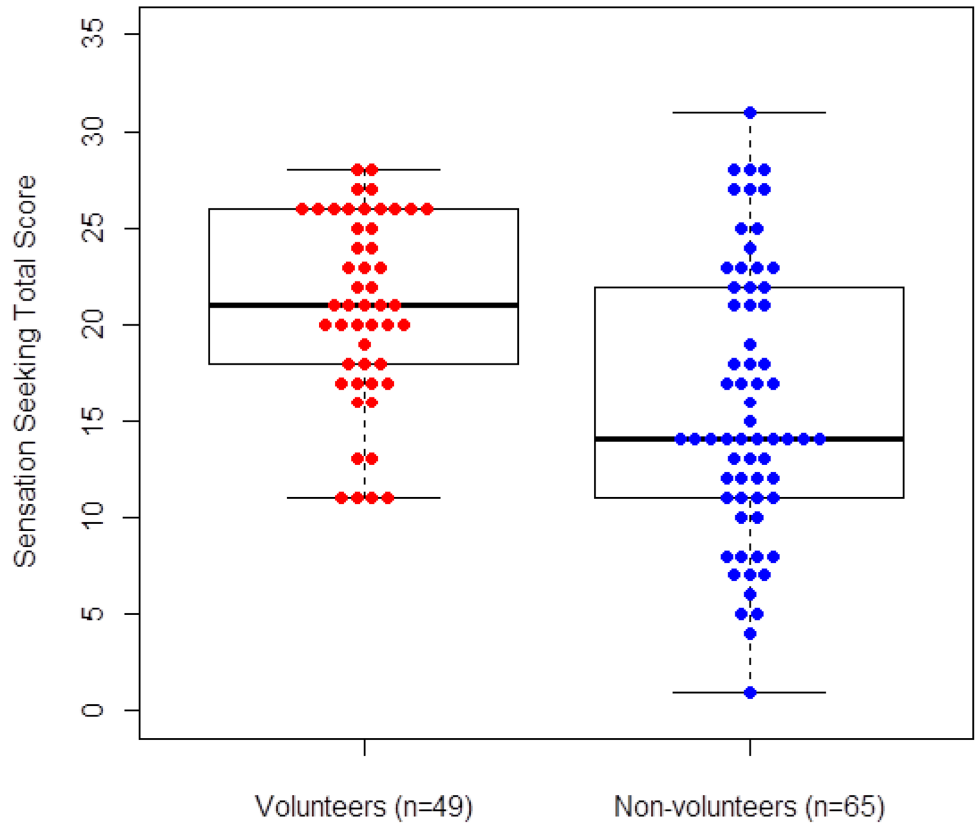

Figure 2.
Distributions of Sensation-Seeking Scale (SSS) scores in volunteers and non-volunteers.

Table 1

Selected Sample Characteristics

Characteristic	Overall Sample (N=114)	Volunteers (N=49)	Non-Volunteers (N=65)	*p*-value[a]
Gender, N(%)				**0.025**
Male	56(49.1)	30(53.6)	26(46.4)	
Female	58(50.9)	19(32.8)	39(67.2)	
Race, N(%)				0.072
Asian	36(31.6)	10(27.8)	26(72.2)	
Black	38(33.3)	16(42.1)	22(57.9)	
White	34(29.8)	20(58.8)	14(41.2)	
Other	6(5.3)	3(50.0)	3(50.0)	
Age, years	22.9(2.7)	23.1(3.2)	22.8(2.3)	0.616
Education, years	15.4(2.0)	15.1(2.4)	15.6(1.7)	0.178
Drinks per week	1.4(2.0)	1.6(2.5)	1.1(1.6)	0.216
NEO Neuroticism	52.0(6.1)	51.6(6.0)	52.3(6.3)	0.567
NEO Extraversion	42.6(5.8)	43.3(5.7)	42.1(5.9)	0.273
NEO Openness	48.3(5.8)	46.5(5.5)	49.7(5.6)	**0.004**
NEO Agreeableness	40.9(6.3)	41.7(6.1)	40.3(6.4)	0.262
NEO Conscientiousness	44.4(4.4)	44.7(4.76)	44.1(4.1)	0.456
NEO Impulsiveness	50.6(7.8)	48.7(6.5)	52.0(8.5)	**0.030**
NEO Values	38.5(7.6)	36.8(7.0)	39.7(7.8)	**0.042**
NEO Competence	40.7(6.7)	42.3(7.6)	39.5(5.6)	**0.027**
Impulsivity (BIS)	56.7(9.8)	57.5(10.6)	56.1(9.1)	0.434
Sensation-Seeking (SSS)	18.0(6.7)	20.9(4.9)	15.8(7.0)	**<0.001**
SPSRQ Punishment	7.0(4.6)	6.4(4.1)	7.4(4.9)	0.229
SPSRQ Reward	9.4(4.1)	9.7(4.3)	9.2(4.1)	0.583
IMT Ratio	0.30(0.2)	0.33(0.2)	0.28(0.2)	0.074
DMT Ratio	0.33(0.2)	0.37(0.2)	0.30(0.2)	0.058
GoStop Ratio150msec	0.3(0.3)	0.3(0.3)	0.3(0.3)	0.991
TCIP Immed. Choices	12.8(13.4)	13.4(12.8)	12.4(13.9)	0.693
TCIP Delayed Choices	24.1(16.6)	22.1(15.7)	25.6(17.2)	0.270
SKIP Longest Delay	270.8(295.7)	308.4(328.0)	241.1(266.3)	0.235
SKIP Total Responses	223.4(597.9)	217.0(576.0)	228.5(619.3)	0.921
IGT Net Total	16.5(24.7)	14.5(25.8)	18.0(23.9)	0.454

NOTE: Values represent means and standard deviations except where indicated otherwise.

[a]Differences between volunteers and non-volunteers

p-values <0.05 are in bold.

Table 2

Pairwise correlations among variables with significant bivariate effects on volunteerism

Variable	1	2	3	4	5	6	7	8	9
1. Sensation-Seeking (SSS Total)	--								
2. SSS Thrill & Adventure	0.7103 ***	--							
3. SSS Experience-Seeking	0.7553 ***	0.3698 ***	--						
4. SSS Disinhibition	0.7769 ***	0.3382 ***	0.4497 ***	--					
5. SSS Boredom	0.668 ***	0.2079 *	0.4082 ***	0.4938 ***	--				
6. NEO Openness	−0.2384 *	−0.0789	−0.1738	−0.3095 ***	−0.1427	--			
7. NEO Impulsiveness	0.0458	0.1453	−0.0069	−0.0125	−0.0266	0.1079	--		
8. NEO Values	−0.236 *	0.0515	−0.3434 ***	−0.2704 ***	−0.1759	0.4564 ***	0.198 *	--	
9. NEO Competence	0.1939 *	0.1286	0.053	0.1323	0.2803 ***	0.003	−0.071	−0.1389	--

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$

Table 3

Estimated Odds Ratios for Characteristics that Predicted Volunteer Status

Characteristics	Crude OR[a] (95% CI)	*p*-value	aOR[b] (95% CI)	*p*-value
Gender				
Male	1.00(reference)		1.00(reference)	
Female	0.42(0.20, 0.90)	0.026	0.60(0.23, 1.57)	0.303
Sensation Seeking	1.14(1.07, 1.22)	<0.001	1.11(1.03, 1.19)	0.008
NEO Openness	0.90(0.83, 0.97)	0.006	0.91(0.83, 1.01)	0.066
NEO Impulsiveness	0.94(0.89, 1.00)	0.035	0.92(0.86, 0.98)	0.016
NEO Competence	1.07(1.00, 1.13)	0.031	1.06(0.99, 1.13)	0.098
NEO Values	0.95(0.90, 1.00)	0.046	1.01(0.94, 1.08)	0.824

[a]Crude OR: odds ratio; 95% CI: 95% confidence interval;

[b]aOR: Adjusted OR, adjusted for covariates included in the table