PERSONALITY FACTORS AND TRUST IN PLACEBO MEDICAL TRIALS

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Prior research has reported that individual differences influence both placebo and nocebo responses. The present study examined how individual personality, as well as trust, influence placebo/nocebo belief and symptom reporting after receiving an inert capsule that for some was described as an active "cognitively-enhancing" trial medication. Individuals (N = 104) were randomly assigned to one of three conditions: condition A participants were told they'd received the medication, condition B participants were told they'd received a placebo, and condition C participants were told, via random assignment, each would receive either the medication or placebo (after the experiment this condition listed the group – medication or placebo - each believed s/he was in). The study was completed in the UNT Student Health and Wellness Center to provide context in a medical setting. Of the 104 participants, 46 (44.2%) were either placed by experimental design or self-report in the medication group. Participants with a belief in medication ingestion, regardless of condition (i.e., A or C), reported significantly more symptoms (M = 16.65, SD = 3.178), than participants who believed they had ingested a placebo (M = 14.21, SD = 2.58), t (102) = 4.32, p = .001.

Aspects of Neuroticism and Extroversion, as well as trust were correlated with symptom reporting and/or placebo/nocebo responses. It appears that that personality is part of a combination including trust, context and expectations. It is recommended that future research on personality and placebo effects consider the role of individual factors, context and communication of expectations.

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INTRODUCTION

Introducing the Five-Factor Model

Personality involves the study of the whole person, and everything that is important about the individual and the individual's psychology (Funder, 2007). When considering this definition, defining "wholeness" and "everything" becomes problematic. We circumvent these problems by choosing several different approaches to studying personality. Learning approaches, trait approaches, psychoanalytic approaches, and cultural approaches are a few examples. Within each approach a theory or set of theories exist to explain an individual's personality of the individuals set of personality characteristics.

Determinism is concerned with principals of the source or the cause of certain behaviors or responses. Deterministic principles assume that everything that happens has an identifiable cause and/or reason. Brenner (1974) labeled the deterministic approach of psychology psychic determinism. For example, Freud believed the root of personality was the unconscious and subsequent conflicts between the individual's reality and the individual's unconscious urges. These conflicts are what shape the individual, i.e., how we think, act, feel, and believe (cognitions, behaviors, emotions and values). Examining psychic determinism from a personality standpoint, these unconscious conflicts influence our thoughts and actions, thus forming our personality. While Freud's psychic conflicts - the id, ego and superego are far from empirical measures of personality characteristics, his theory does create a strong basis for starting to examine personality based on observable behaviors and thoughts.

Another approach is the biological approach. This approach examines neuroanatomy and neurochemistry to determine how we behave and our subsequent development and presentation of personality characteristics. The research in this area is vast, complex and often contradictory

but some conclusions can be drawn (Funder, 2007). One conclusion is that multiple brain structures interact to influence personality and within these structures the chemical balance of neurotransmitters and hormones are important. The structures typically associated with personality, not to mention most other biological tenants in psychology, are the thalamus, hypothalamus, amygdale, hippocampus and frontal cortex. The amygdale and hippocampus are especially important given their relation to emotion and memory. These structures, along with the frontal cortex, influence how we think, anticipate and reason. The complexity of the interaction of the brain structures and how they influence our personality is important considering how we treat disease and illness.

Antonio Egas Moniz demonstrated the frontal cortex did indeed influence personality. Moniz (1964) reported that injecting alcohol into the prefrontal cortex (one of many forms of prefrontal lobotomy) could indeed change someone's personality. Similarly, Bejjani et al. (1999) demonstrated personality change by initiating depression symptoms by stimulating the substantia nigra in Parkinson's disease patients, an area strongly associated with dopamine regulation in the brain. Eysenck (1967, 1987) tried to tie two personality characteristics, extraversion and introversion, to neuroanatomy. Eysneck proposed activity within the ascending reticular activating system (ARAS) determined whether someone displayed introverted versus extroverted personality traits. Zuckerman (1991, 1998) both supported and disproved Eysenck's theory of personality and neuroanatomy by showing multiple regions in the brain including the ARAS are involved in the display of personality characteristics. Zuckerman's findings again demonstrate the complexity of both the brain and an individual's personality characteristics.

The aforementioned studies measured personality based on the two typology or trait model. Common sense, however, dictates that a person cannot be divided based on binary logic

or yes or no questioning. Formal personality assessments are performed by means of either a projective, objective, or subjective (expert interview) technique, all of which assume multiple constructs, both physiological and psychological, are at work. Any assessment technique must exceed a standard set by what is referred to as the Barnum effect (Andersen & Nordvik, 2002; Dickson & Kelly, 1985). The Barnum effect dictates that, like any scientific measure, personality assessment must predict behavior better than chance and be based on some form of valid methodology. Valid methodology, as in most sciences, is the key to developing a sound understanding of any abstract or theoretical construct.

Personality assessment is often very complex, in that researchers are measuring a hypothetical construct. As of the early 2000's, the Five Factor Model best describes the dimensions of personality in a "normal" population (Ellis & Abrahams, 2009). The five factor model of traits is not the only way to examine personality. A two factor (Block, 2001), a three factor (Eysenck, 1991, 1992, & 1994), a four factor (Brown, Strong, & Rencher, 1974), and a sixteen factor (Delhees & Catell, 1970) model all exist as methodological measures of personality. One goal of personality measures is to create an omnibus yet parsimonious inventory, to measure a wide range of traits or characteristics. The five factor model, also known as the "big" five, is thought to be this measure. Lewis Goldberg coined the term the Big Five after reviewing the consistency of findings that five factors accounted for the majority personality traits (Ellis & Abrahams, 2009).

During the 1980's, a variety of sampling methods and cultural samples lead to a five-factor model which best fits across ratings techniques, personality measures, and cultures (John, 1990; McCrae & Costa, 1987; Peabody & Goldberg, 1989). Through the use of factor analysis of adjectives and descriptions, the personality traits Openness, Conscientiousness, Extroversion,

Agreeableness, and Neuroticism have been developed as the Big Five. The Big Five has also been found to be stable and reliable across a lifetime (McCrae & Costa, 1994). The ideal of stability in personality adds an abstraction to the idea of personality.

The consistency paradox would argue that while personality ratings across time among different observers are consistent, behavioral ratings of a person across situations are not consistent (Mischel, 1968). Research has shown if an individual brings a particular disposition to a specific situation then s/he will behave in a particular way (Mischel & Shoda, 1995). Considering these findings, a person should behave in a particular way in medical settings e.g., report symptoms and other relevant information regardless of situation. Among other things, personality traits likely influence symptom reporting, placebo beliefs, and the level of trust and subsequent communication between patients and doctors within the medical context. If a "placebo-responder" exists s/he should have a stable personality profile which creates the disposition to respond consistently in a medical context to a medical provider.

Symptom Reporting and Placebos

Barondess (1979) refers to illness as an individual's subjective experience of suffering while disease describes actual physical pathology. Barondess went on to suggest that self-report measures are more accurate illness measures, rather than disease measures. Self-report symptom measurements are important to accurately diagnosis and treat both illness and disease. No model exists to accurately describe who is more likely to self-report symptoms. An assumption exists that multiple constructs influence self report, and expectancies exist which govern how symptoms are both reported and presented to health care providers.

On a macro level, culture greatly influences not only the extent but the nature of symptom reporting (Harlap et al., 1975; Zola, 1966). The individual who seeks any form of treatment has always been an issue in treatment recommendations and considerations. Socioeconomic status, a measure of culture, has shown that ethnic disparities exist in our culture and is related to health, health outcomes and health care. Within the field of health disparities, Myers and Hwang (2002) proposed a biopsychosoical model to explain why symptom reporting and treatment seeking behaviors vary among cultures. The authors argue that sociocultural factors and biological factors interact over time with psychosocial adversities. They further hypothesize that personality characteristics such as neuroticism and pessimism serve as psychological vulnerabilities to health and health related outcomes. The model purports that other psychological characteristics such as dispositional optimism and perceived control (Eizenman, Nesselrroade, Featherman, & Rowe, 1997) can moderate risk associated with health. The two previous studies indicated that a psychological construct does indeed influence health.

Whitehead, Winget, Fedoravicius, Wooley, and Blackwell (1982), examined individual symptom reporting behaviors based on past experience and expectations. The researchers discovered that individuals who could be characterized as displaying chronic illness were more likely to recall receiving rewards when sick as a child. Learning principles, including operant conditioning, have been used to explain individual and cultural differences in symptom reporting. This creates a strong foundation for how expectations influence not only how we report symptoms but our overall general health outcomes.

Distraction strategies are effective for reducing pain perception when the pain is mild in intensity and the experience of pain is brief (McCaul & Malott 1984). The competition for cues hypothesis states that only a limited amount of sensory input can be consciously processed

(Navon & Gopher, 1979). The things we pay attention to consciously, have an effect not only on what we perceive but what we report perceiving, i.e. we can only report symptoms we attend to. The absence of symptoms may not mean they are truly absent and *vice versa*. A big component of what we perceive is based on our personalities and what we are attuned to as individuals. With classical conditioning and reinforcement strategies, over time we may notice cues which provide the most rewards or the highest amount of symptom reduction.

Pennebaker, Colder, and Sharp (1990) and Taylor (1999) demonstrated that participants willing to disclose emotionally traumatic experiences develop fewer somatic complaints. Negative emotions associated with anxiety can cause individuals to increase their monitoring of internal processes (Wegner & Giuliano, 1980) and can contribute to disease development, while positive emotions have been related to a decrease in disease symptoms (Vaillant, 1976). An increased focus on negative emotions will inevitably lead to more somatic complaints. A proposed explanation for increased symptom reporting is a decrease in homeostatic functioning, which in turn is due to an increase in allostatic load. In any case, negative emotions not only affect symptom reporting, but they also seem to affect overall health. A long standing assumption is that anxiety and negative emotions are experienced more often by neurotic individuals (as measured by personality inventories). Thus one can surmise the personality again plays a significant role in symptom reporting and overall health.

The standard biomedical model places disease development within a linear causal process. Lovallo (2005) states the traditional medical model has four main characteristics influencing the linear model: one-way causation, a physiological process, nonheirarchial structures, and a dualistic nature. The disease and subsequent symptom reporting is due to a pathogen acting upon the host in some form of a physiological process known to the host through

symptom reporting. The mode of therapy is a direct physical intervention to restore homeostasis and work to cure the individual (Lovallo, 2005).

Absent from this model are aspects known to have direct effects on health outcome, as well as the communication process associated with symptom reporting. Perceived and actual stress levels, are two such aspects that directly affect health outcomes. Other components such as physician trust or patient expectations are likely important as well. The standard biomedical model may not fully consider cognitive functions related to thoughts and emotions as an influence on health and well being, often ruling out multiple psychological processes when considering treatment.

Within the medical model, “inert” therapies sometimes produce effects. These effects may be positive (e.g., a reduction in pain) and are labeled placebo effects. Conversely, the effects may be negative (e.g., an increase in pain) and are labeled nocebo effects. “Placebo effects” is the generic term used when discussing any of these therapies, regardless of positive or negative outcome. The mechanisms for why and how placebos work is the focus of much research. Context, environment, personality, expectancy, and conditioning have all been addressed as playing a role. Within the medical model a placebo effect implies that the physiological effect based on treatment has to do with an alternate mechanism, possibly the influence of a psychological mechanism. Lovallo (2005) and Harrington (1997) place placebos/nocebos within the medical model as having direct influence on the disease state without a known mechanism for this direct influence.

Expectancy and the Conditioning of Placebo Beliefs

Expectancy theory and conditioning principles have long been thought to provide answers as to why individuals respond to placebo treatments (Bjorkedal & Flaten, 2011, Geers, Helfler, Weiland, & Kosbab, 2006, Geers, Helfer, Kisbab, Weiland, & Landry, 2005, Benedetti, 2002, Price, et al. 1999, Montogemry & Kirsch, 1997). Expectancy is defined as a person's subjective belief that a particular outcome will occur in response of a stimulus. Kirsch & Baker (1993) proposed response expectancy as a cognitive mediating mechanism in the conditioned placebo response. A review provided by Stewart-Williams & Podd (2004) argues expectancy and conditioning are a compatible approach to examining placebo belief further supporting Montogemry and Kirsch, (1997).

A combination of expectancy and conditioning, as a way to understand placebo effects is expected, given our culture's reliance on modern medicine. Modern medicine typically ascribes to an allopathic approach, the biomedical model, thus a linear cause, process, and outcome. If something hurts, i.e. symptoms are present, professionals will locate and treat them either by pharmacological intervention or health related advice, and health will improve. Society is conditioned to expect symptom relief from medical treatment in a medical context.

An example is provided by Flaten et al. (1999.) The researchers divided participants into three drug-information groups: those who were informed they would receive a relaxant, those informed each would receive a stimulant, and those given no drug information. The three groups received a muscle relaxant as administered in a double blind method by uniformed nurses in a medical context. Results indicated when participants were informed to expect a stimulant and thus more tension, they reported greater tension even when receiving an active muscle relaxant. Increased tension in the group receiving stimulant information represents a nocebo response

based on the influence provided information (Flaten et al. 1999). While this study indicates that conditioning and expectancy exist in medical context, it should be noted that individualism also exists in these contexts. As such, it is important to determine who is most likely to benefit from these components of medical treatment, as well as the importance of the role of communication between clinician and patient.

The Doctor-Patient Relationship and Sickness Communication

The doctor-patient relationship is often poorly defined and fragmented in literature while being one of the more important concepts in health care (Ridd, Shaw, Lewis, & Salisbury 2009). What defines a strong doctor-patient relationship differs depending on the medical profession as well as the patient and arguably, the illness/disease. In the medical profession, a trusting relationship between a patient and a physician may lead to an increased comfort level and belief in the knowledge that the provider is communicating to the patient. Measuring the various aspects of this relationship can better aid in understanding patient placebo/nocebo symptom reporting and possible placebo belief.

A physician's type of communication and skills are often assessed and used as an empirical measure of the doctor- patient relationship (Palmboom, Willems, Janssen, & de Haes, 2007). The purpose of communication within health care is to create a good interpersonal relationship, exchange information, and make treatment-related decisions, all with the aim of positive health outcomes. Placebo responding may rely on communication more than has been examined in research. An element of symptom reporting is strongly related to communication about symptoms either in the past (conditioning) or the present (expectations). The perception of the interpersonal relationship and the exchange of information is a key component to the belief

an actual treatment has occurred, in absence of any real treatment. In fact, a recent (2011) NIH study revealed that nearly 50% of active physicians report giving their patients placebos (Fent, Rosemann, Fassler, Senn and Huber, 2011).

Stewart (1995) examined doctor-patient communication and health outcomes with success showing that communication skills do indeed affect patient outcomes. Patient centered communication and treatment centered communication both influence not only health related outcomes but additionally overall patient satisfaction. Further research by Williams, Weinman, and Dale (1998) demonstrates how doctor-patient communication influences patient satisfaction based on information provision, information seeking, affect, and the communication style of the doctor. The first three variables are considered to be an exchange between doctor and the patient that is more in depth than just communication between professional and patient, in that an interpersonal relationship forms. Communication concerning information provision and information reception for both the patient and doctor are aimed at gaining favorable health outcomes. The authors further discuss how the physician's interpersonal skills as measured by affect and communication style contribute to both patient satisfaction and health related outcomes.

Another way to help clarify or defragment patient-doctor relationships is by examining continued care. Patients who chose to continue care with a physician will likely report that a strong relationship exists; one in which some form of an interpersonal bond has developed. Such a bond influences the patient's belief about the level of care received. These beliefs about care level are not always well defined and/or understood by either the patient or the physician. Furthermore the medical model does not always lend itself to explaining the complexities involved in the patient-doctor relationship or the strength of the said relationship.

Saultz (2003) refers to continued care based on strong relationships as interpersonal continuity of care. Defining and measuring interpersonal continuity helps lend an empirical basis for measuring the strength of relationships between patients and providers, as well as symptom reporting and subsequent health related outcomes. Interpersonal continuity helps examine not just the relationship, but the degree of trust involved as well. A patient who continues to seek care on a continuous basis and communicate with a health care professional has likely developed a high level of some form of trust with the professional. Longitudinal care does not necessarily guarantee the depth of a patient-doctor relationship or continuity of care (Ridd, Shaw, Lewis, and Salisbury, 2009) but it does still play a role in the exchange of information and the patient's beliefs about his/her symptoms. Expectations or social conditioning of trust based on one instance of longitudinal care may translate from health care provider to health care provider and influence overall trust in both the doctor and the medical profession.

Characteristics of the doctor-patient relationship, such as trust, seem to be a better predictor of symptom reporting and overall health outcome as compared to length of care. The role of trust has been examined in the development and maintenance of interpersonal relationships within the medical setting and with the medical field (Zheng, Hall, Dugan, Kidd, and Levine 2002; Mechanic 1996; Pellegrino, Veatch, and Langan 1991; and Parsons 1951). Trust, as defined within a medical setting, has both intrinsic and instrumental components when examining communication as related to treatment; (Hall, 2006; and Rhodes and Strain 2000) and it has proven to be a defining element in any interpersonal relationship, particularly in the doctor-patient relationship (Pearson and Raeke 2000).

Trust in the Medical Profession

Trust as a concept/construct can be defined as an element of uncertainty and the level of risk associated with an individual's uncertainty regarding the motives, intentions, and future of another on whom the individual is reliant (Mirshra, 1996). Trust is a multidimensional construct that is described across various academic disciplines (Pearson and Raeke, 2000), and can vary from context to context as do the conditions that may or may not elicit trust (Rose-Ackerman, 2001).

Trust, as measured within the medical context, is often defined in one of two ways. Anderson and Dedrick (1990) and Thom, Hall, and Pawlson (2004) both examine trust as a set of beliefs or expectations that a physician will provide medical care in a certain manner to increase health related benefits. Trust examination based on this definition has an instrumental value important to both the psychological and physiological therapeutic relationship. A second way to define trust within the medical realm involves examination of the interpersonal relationship between patient and physician (Caterinicchio, 1979). Regardless of definition, the health care setting, often containing a degree of uncertainty and risk, requires development of trust from patients in their respected providers (Alaszweski, 2003). The development of trust in physician competence leads to a stronger belief that the symptoms being described will be received and the advice about side effects or expected changes in health is more accurate and beneficial.

Physician behavior can be generally divided into five dimensions thought to influence trust: competence, compassion, privacy and confidentiality, reliability and dependability, and communication (Mechanic and Myer (2000); Mechanic and Schlesinger, 1996; and Andersen and Dedrick, 1990). Each of these dimensions/behaviors is thought to influence trust in the physician and subsequent care. Each of these behaviors is directly related to the interpersonal

trust that is related to vulnerability associated with being ill and the inequality of the doctor-patient interpersonal relationship (Calnan, 2004).

Another aspect directly related to trust is patient involvement. Patient involvement in the doctor-patient relationship will directly influence the communication process and subsequent informational exchange between patient and doctor. Patient trust and active participation are desirable for building the relationship as well as associated with improved health outcomes (Trachtenberg, Dugan, and Hall 2005). Paradoxically, too much trust may be negative and patients should be careful to avoid a paternalistic/maternalistic type of care (Gatter, 2004). This may be especially true in managed care settings where the individual may be unable to choose a doctor based on affect, communication, or competencies. The patients trust in a physician may be implied based on an existing set of societal standards or some unknown conditioning principles. Implied trust is again strongly related to social conditioning and the expectation society has developed concerning the health field and the positive benefits associated with treatment.

The patient's attitude is also highly relevant when examining the doctor-patient relationship and the amount of trust present in that relationship. Assertive patients, who are active in communication and care, do not always indicate distrust while passive patient involvement is not necessarily an indicator of trust. Trachtenberg, Dugan, and Hall (2005) suggest that trust may form in relationships where patients are both active and passive participators in the decision making process.

The importance of trust has long been established not only in medicine, but also in psychology, to examine how interpersonal relationships form and are maintained. Trust arguably affects multiple levels of care within the health care profession and a number of therapeutic

interventions both in medicine and psychology. Balkrishnan, Dugan, Camacho, and Hall (2003) suggest the patient's views about particular physicians are not entirely independent from their views about the medical system in general. Furthermore these authors suggest that interpersonal physician trust is based on patient experience(s) and the physicians' characteristics/behaviors, while the patient's underlying preferences, values, and attitudes are more relevant to views about the medical profession. Hall (2006) argues that given the changes in health care in America, trust in the health care field is an important determinant for individual interpersonal trust in physicians. Health care changes and being treated by multiple physicians at once creates a nexus of individual characteristics, context, experience, and expectations that is not easily sorted, defined or empirically measured for research purposes regardless of research topic.

An increased level of trust in the medical profession is associated with relying on the judgment of medical professionals, the patient seeking help, and the patient granting increased control to the physician, following physicians' treatment recommendations and allowing the physicians to make decisions for her/him (Trachtenberg, Dugan, and Hall 2005). While it is unclear how or when a patient increases physician trust, higher levels of trust in the medical profession greatly influences direct care to the patient and will likely influence the patients' thoughts and perceptions about both the treatment effects and symptom reporting.

The trusting patient may sometimes be viewed as gullible, believing anything the physican tells him/her. Rotter (1967) defines interpersonal trust as an expectancy held by an individual that the word, promise, spoken or written statement of another can be relied on. This relates well to symptom reporting considering that written and/or spoken words are the mainstays of medical communication.

Rotter (1980) states that individuals who are high trusters are not more gullible, and further states high trusters are no less capable of determining who should be trusted or should not be trusted when compared to an individual who is referred to as a low truster. Rotter (1980) further reports that trust can become a generalized expectancy and can be shared with respect to situational specificity. A generalized expectancy is governed by not only the situation but overall experience(s). It has already been discussed how expectancy plays a key role when considering the medical field, placebo belief, and symptom reporting.

Measurement of trust in a medical context has great implications when considering the doctor-patient relationship. Mechanic (1998) argues trust is alone important for its therapeutic effects for the patients. A review of the literature by Calnan and Rowe (2004) reveal not enough evidence exists to conclude that trust directly affects health outcomes. However, the authors reveal the empirical evidence implies that trust seems to mediate the therapeutic process between doctor and patient and has indirect influence on health outcomes. Furthermore, trust is highly correlated to patient satisfaction (Thom and Ribisi, 1999).

Purpose of Research

Patient satisfaction and trust have been examined with the findings that multiple types of trust exist that are distinct from patient satisfaction (Thom, Ribisl, Stewart, and Luke 1999). Patient satisfaction, communication, and trust all influence the health related outcome but vary depending on the purpose of treatment and the observer. This opens the door for an individual element such as personality type that can/needs to be accounted for to better understand how people's individual symptom reporting and belief in treatment is influenced by trust and communication. Wasylikw and Fekken (2001) did indeed show that personality dimensions are

strong predictors of general measures of health and health behavior while personality traits are strong predictors of specific measures of health behaviors. These findings show that regardless of dimension or trait, personality does indeed factor into health and health related behaviors.

Measuring trust within the medical context can help shed light on why some individuals are more likely to report symptoms associated with placebo/nocebo beliefs. If strong expectancies related to beneficial treatment and care exists within the medical context, trust is likely to influence actual physiological symptoms and the perception of physiological symptoms. Individuals who trust in doctors at a higher level are more likely to be influenced by the knowledge provided by a doctor concerning symptoms, diagnosis, and treatment.

Previous research by Geers, Helfer, Kosbab, Weiland, and Landry (2006) and Baker, Kelly, and Kauffman (2010) have shown that personality does indeed influence both symptom reporting and placebo/nocebo belief. Placebo research based on personality correlates is sparse within its self. To date no research combines placebo/nocebo belief, symptom reporting, personality correlates, and trust. Furthermore, little research exists combining the five factor model, trust, and health related outcomes. Health related research within the medical field is often methodlogically flawed and abundant in measurement instruments with substandard psychometrics. Examining these four variables within a medical context can help clarify not only symptom reporting, but symptom perception in general, especially considering no one actually receives an active substance in placebo research.

Communication and trust are the key components to a strong relationship within the medical profession and the relationship with a particular medical professional. The direct effects of communication of expected outcomes and trust as both an intrinsic trait and instrumental

component on reported health outcomes is not fully understood nor accounted for within the medical model.

Research Questions

1. Based on earlier research, (Haggard, Kelly, & Forrer, 2003; Link et al. 2006), it is hypothesized that participants will report symptoms following placebo ingestion.

2. Based on previous research, (Baker, Kelly, and Kauffman, 2010), it is hypothesized (a) that self-reported characteristics of the personality factor "openness" will lead to an increase in symptom reporting and (b) belief of having received the trial medication [as opposed to a placebo].

3. Based on Costa and McCrae (1987), it is hypothesized that an increase in self-reported level of neurotocism will lead to (a) an increase in nocebo symptom reporting and (b) overall symptom reporting.

4. It is hypothesized that and increased level of trust in the medical profession will lead to an increase in (a) symptom reporting and (b) an increased belief in medication receipt.

5. It is hypothesized that and increased level of trust in medical research leads to an increase in (a) symptom reporting and (b) an increased belief in medication belief.

6. It is hypothesized that high levels of both types of trust and high levels openness will influence symptom reporting based on medication (versus placebo) belief.

METHOD

Participants

Participants included 104 UNT students, 18 years or older who could read and write in the English language. There were no other exclusionary criteria. Participants were recruited through the Psychology Department's research website and were compensated for participation with course credits. The study was submitted to UNT's Institutional Review Board and received approval.

Methods

Participants responded to an experimental announcement on the University's Psychology department Research Participation Pool website. The announcement was titled, "Cognitive Tasks and Medication Performance", and was accompanied by a brief description of purpose: "to study the effectiveness of a fast-acting trial medication intended to enhance mental performance." The University of North Texas Student Health and Wellness Center (UNTHWC) provided a room, commonly used for patient treatment, for study use.

Each participant arrived at the UNTHWC and checked in with a receptionist at the front desk. The investigator met each participant in a common waiting room used by those seeking medical treatment. The investigator mirrored other members of the HWC staff by wearing a white lab coat and a HWC identification badge, standard for all employees.

Measures

Demographic Information

Demographic and health behavior variables including age, gender, ethnic background,

number of physician visits, use of prescription medications, vitamins, and herbal supplements were obtained. Supplying such information is consistent with healthcare practice, and was included only to reinforce the medical context and for possible future analysis.

NEO-PI-3

Personality was assessed with the NEO–PI–3, a 240-item self-report measure of the five major personality facets (N =neuroticism, E = extroversion, O = openness, A = agreeableness, C = conscientiousness). The NEO-PI-3 is normed for use with a non-psychiatric population. The facets of the five-factor model of personality are assessed using a 5-point Likert scale ranging from 0 (*strongly disagree*) to 4 (*strongly agree*). The NEO–PI–3 yields composite scores for each personality factor with six supplementing facet scores for each of the five personality factors characteristics. Each personality facet is numbered according to the facet representation within each personality factor. The NEO-PI-3 is available in two versions: Form S, the self-report, and Form R, a third party rating. Form S was used in the present study. Internal consistency coefficients for the five facets of Form S, measured in a large sample of adults, range from .89 to .93 (Costa & McCrae, 2010). The test–retest reliability coefficients for the NEO-PI-R over a 3–6 year period ranged from .63 to .83 for both self-reports and third party spouse ratings (Costa & McCrae, 1988). There are currently not test-retest reliability but the NEO-PI-3 is estimated to be comparable to the NEO-PI-R due to high similiarity (McCrae, Kurtz, Yamagata, & Terracciano, 2011)

Ravens Progressive Matricies

The Raven Progressive Matricies is composed of five sets of diagrammatic puzzles that

change in dimension and increase in difficulty. Each set consists of twelve puzzle matrixes, each of which is thought to test the ability to grasp the methods required to solve them. The Ravens Progressive Matricies are thought to measure a person's capacity for intellectual activity, especially fluid intelligence. Internal consistency coefficients for the five sets .90 to .99 (Raven, Raven, & Court, 2000). The test-retest reliability coefficients have been .83 at a one year follow up and up to .91 following shorter intervals (Raven, Raven, & Court, 2000).

Placebo/Nocebo Questionnaire

The questionnaire included a 3-point scale where 1 = *not at all*, 2 = *a little/some*, 3 = *a lot/much*. Participants indicated whether, or to what extent, each of the 12 placebo/nocebo responses was experienced following capsule ingestion (see below for a list of the possible "side effects" of the supplement).

Trust in Medical Profession

The Trust in the Medical Profession questionnaire is 11 items in which participants will respond to a Likert scale scored 5 for *strongly agree* to 1 for *strongly disagree*. Negatively worded items (2, 7) are reverse scored for use. In a US national sample of 502 adults, the mean is 33 with a standard deviation of 6.9 and a Cronbach's alpha of .87 (Hall, 2006).

Trust in Medical Research

The Trust in Medical Research is a 12 item questionnaire scored using a Likert scale also scored 5-1, *strongly agree* to *strongly disagree*, with negative items (3, 5, 8, 11) reverse-coded.

In a sample population of 124 adults, the mean is 36.25 with a standard deviation of 7.83 and a Cronbach's alpha of .87 (Hall, 2006).

Procedure

Upon arrival and retrieval of a student participant, the investigator led each participant to a medical observation room. The location of the study and the aforementioned details of the investigator's dress were intended to add to the perceived legitimacy of a "clinical trial." A pill cup with a capsule was present upon entrance into the observation room. Participants were asked to read one of three experimental information sheets (Form A, B, or C described below) and a consent form prior to providing consent. The experiment information sheet explained that participation included receiving a fast acting trial medication, a placebo, or a placebo/fast acting trial medication (randomly determined). In reality, each participant received an inert placebo capsule filled with corn starch.

Form A

> Each participant in this study will receive either a fast acting trial medication or a placebo. Both will be administered in capsule form. **You will receive the trial medication.** The medication is being tested to determine if it enhances cognition (i.e., mental abilities). The medication contains no ingredients that are known to interact with prescription or over-the-counter medication. Because corn products are used in the production of both the medication (an inactive ingredient) and placebo capsules, please inform the researcher if you have ever had an allergic reaction to corn products. Any effects of the medication will be short-term.

Form B

> Each participant in this study will receive either a fast acting trial medication or a placebo. Both will be administered in capsule form. **You will receive the placebo during this trial as part of a control group.** The medication is being tested to determine if it enhances cognition (i.e., mental abilities). The medication contains no ingredients that are known to interact with prescription or over-the-counter medication. Because corn products are used in the production of both the medication (an inactive ingredient) and

placebo capsules, please inform the researcher if you have ever had an allergic reaction to corn products.

Form C

Each participant in this study will receive either a fast acting trial medication or a placebo. Both will be administered in capsule form. **You will receive either the trial mediation or the placebo during this procedure.** The medication is being tested to determine if it enhances cognition (i.e., mental abilities). The medication contains no ingredients that are known to interact with prescription or over-the-counter medication. Because corn products are used in the production of both the medication (an inactive ingredient) and placebo capsules, please inform the researcher if you have ever had an allergic reaction to corn products. Any effects of the medication will be short-term.

All information sheets included a list of twelve known side effects that "may result from the trial medication". Six of the twelve effects include desired benefits (i.e., placebo responses): elevated mood, improved memory, clearer thinking, increased mental alertness, enhanced sensory perception, and increased energy levels. The remaining six effects listed were undesirable side effects (i.e., nocebo responses): sensitivity to bright lights, dry mouth, headache, fatigue, allergic reaction such as itching of the skin, and mild gastrointestinal disturbances. After signing the consent form, the experimenter inquired about any known allergies to medication, again to provide context. Each participant was provided with water and asked to ingest the capsule.

After ingesting the pill, the experimenter presented the participant with one questionnaire at a time and provided brief instructions. The participant was first given the demographics questionnaire. In order to add to the guise of a medical study, the experimenter took a moment to "follow-up" the demographics questionnaire by scanning and questioning responses associated with the items concerning over-the-counter, prescription medications, vitamins, and herbal supplements. The participant was then given the NEO-PI-R and instructed on how to fill out the questionnaire.

Upon completion of the questionnaire packet the participant was provided a distracter task identified as a "Cognitive Measure" (The Ravens Progressive Matricies). Participants were

told the task would allow for testing of any “mental enhancement” of the medication. Completion of the two questionnaires typically took less than 20 minutes with the experimenter always allowing a full 20 minutes to pass before each participant is instructed to begin the distracter task. After 10 minutes, the experimenter signaled task completion and administered the symptom questionnaire. The participant was instructed to complete the questionnaire based only on the time since ingesting the capsule.

Upon completion of the symptom questionnaire the participant was asked to complete the trust questionnaires. Lastly, each participant was debriefed and remaining questions were answered.

RESULTS

Group Characteristics and Symptom Reporting

Of the 104 participants 35 were in the medication group, 34 in the placebo group, and 35 in the "random assignment" group. Of the 104 participants, 46 (44.2%) were either placed by experimental design or self-report in the medication group. Symptom reporting was as follows: dry mouth, 24%; clear thinking, 51%; headaches, 10.6%; increased mental alertness, 46.2%; fatigue, 22.3%; enhances senses, 32.6%; allergic reaction, 4.8%; increased energy level, 29.8%; mild gastrointestinal disturbance, 12.5%; elevated mood, 28.8%; sensitivity to bright lights, 8.7%; and improved memory, 27.9%.

Preliminary analysis of symptom reporting revealed 74% of the participants reported experiencing at least one symptom related to capsule ingestion (χ^2 (1) = 4.9, p = .02) regardless of belief about capsule content or experimental group. Just over 63% reported experiencing at least one placebo symptom and 48.1% reported at least one nocebo symptom associated with the capsule, with clearer thinking and dry mouth being the most common placebo and nocebo symptoms, respectively. Also, participants with a belief in medication ingestion, regardless of group, reported significantly more symptoms (M = 16.65, SD = 3.178), than participants who believed they had ingested a placebo (M = 14.21, SD = 2.58), t (102) = 4.32, p = .001.

Overall Symptom Reporting and Personality

Overall, Openness was not correlated with Symptom Reporting (p = .239). Examination of personality facets revealed a significant correlation between individuals who reported one or more placebo symptoms and two facets of openness: aesthetics (O2; r = .214, p= .029), and

actions (O4; *r = .211, p= .031).* These same two facets were also correlated with total symptoms reported: aesthetics (O2; *r* = -.195, *p* = .047), and actions (O4; *r* = -.225, *p* = .02).

The correlation with Neuroticism and total symptoms reported approached, but was not, significant (*p*= .072.). A relationship did exist between Neuroticism and total nocebo symptoms reported (N), *r*= .228, *p*= .02). Examination of the personality facets of Neuroticism revealed a significant role of anxiety in symptom reporting: placebo symptoms and anxiety (N1; *r* = .196, *p*= .045), nocebo symptoms and anxiety (N1; *r* = .205, *p*= .037), total symptoms reported and anxiety (N1; *r* =- .240, *p*= .014).

When examining overall Extraversion and total symptoms reported, a correlation did not exist (*p*= .09). A relationship was noted between Extraversion and total placebo symptoms (E), *r*= .227, *p*= .02). Examination of personality facets of Extraversion revealed a significant correlation between individuals who reported one or more placebo symptoms and a single facet of extraversion: positive emotions (E6; *r* = .206, *p*= .004). The same facet also revealed a significant correlation with total symptoms reported (E6; *r* =- .207, *p*= .02).

Placebo/Nocebo Symptom type Reporting and Neuroticism

When examining the individual facets of Neuroticism and symptom type reported, a positive correlation existed between reported anger (N1) and mild gastrointestinal disturbance (nocebo), *r* = .207, *p* = .033. Depression (N3) significantly correlated with headache (nocebo), *r* = .216, *p* = .027 and fatigue (nocebo), *r* = .197, *p* = .045. Impulsivity (N5) significantly correlated with both sensitivity to light (nocebo), *r* = .194, *p* = .048, and fatigue (nocebo) *r* = .198, *p* = .044. Vulnerability (N5) correlated significantly with increased reporting of headaches

(nocebo) $r = .220$, $p = .025$. Total neuroticism was found to be significantly correlated with both headaches $r = .223$, $p = .023$ and fatigue $r = .200$, $p = .042$.

Trust in the Medical Profession and Symptom Reporting

Trust in the medical profession was found to significantly correlate with both placebo symptoms ($r = .221$, $p = .02$), and overall symptoms reported ($r = .212$, $p = .030$). Increased trust in the medical profession was specifically correlated with elevated mood ($r = .168$, $p = .08$), increased mental alertness ($r = .218$, $p = .026$) and increased energy levels ($r = .252$, $p = .01$).

Trust in Medical Research and Symptom Reporting

Trust in medical research was found to significantly correlate with both placebo symptoms ($r = .175$, $p = .07$), and overall symptoms reported ($r = .271$, $p = .005$). Increased trust in medical research was specifically correlated with clearer thinking ($r = .205$, $p = .36$).

DISCUSSION

The present study was successful in replicating earlier findings regarding placebo belief and symptom reporting. Seventy-four percent of participants reported at least one symptom resulting from the ingestion of an inactive substance in capsule form. This percentage included respondents who reported a belief in having ingested a placebo as well as those reporting a belief in having ingested an active medication.

Forty-four percent of the experimental population reported symptoms based on the belief of having received a medication. These participants reported more symptoms than those expressing a belief in having received an inert capsule. The most common placebo symptom reported was clearer thinking and the most common nocebo symptom, dry mouth. A combination of a belief of ingesting an active substance and significantly increased symptom reporting has been replicated five times in our laboratory (Haggard et al. 2003; Kelly & Kinchla, 2005; Link et. al. 2006; Baker, Kelly & Kauffman, 2010). The first four studies included use of an "herbal supplement" (in actuality a placebo capsule) as the experimental focus. This is the first study that includes an "active medication" (in actuality a placebo capsule) in examination in belief/symptom reporting.

The idea of reporting any symptoms based on ingesting an inert substance captures the idea of "placebo-belief", and individuals reporting symptoms based on their perceptions are "placebo-responders." Of interest in the present study are the comparisons between use of an "active medication" as opposed to the "herbal supplement" used in past research (e.g., Baker, Kelly, and Kauffman, 2010). Note in both studies, the list of expected symptoms remained the same. However, in the present study the personality characteristic of Neuroticism replaced the personality characteristic of Openness as having significant effects on symptom reporting. The

supposed use of an active medication more closely approximates clinical trials and the use of a pharmacologically active substance. Thus, this most recent examination likely mirrors results seen in such trials, and may point to the personality characteristics of a placebo responder.

A higher percentage of positive symptoms than negative ones were reported. Participants believing they had ingested the cognitively enhancing medication reported significant increases in clearer thinking, increased mental alertness and enhanced senses. The symptom reporting is interesting when compared to that of a previous study using an herbal supplement placebo (Baker, Kelly, and Kauffman, 2010), where elevated mood, increased energy level and increased mental alertness were reported. Given the expectancy of the use of an active substance (a medication) and the conditioning principles thought to align with the medical model as compared to herbal supplement use and complementary and alternative medicines, the fact that two of three symptoms reported were different is not surprising.

The present study also replicated previous findings in that personality characteristics correlated with symptom reporting and the type of symptoms reported. Unfortunately the experimental group given the option to choose between having received an active medication or placebo typically chose the placebo, thus making any comparisons between the aforementioned few selecting “medication” and those told specifically they’d received the “medication” impossible. It would be interesting to note if personality differences correlated with symptoms when comparing responses of those told they received the “medication” as opposed to those who believed they had.

The present study is the second successful attempt, and the first replication of, research using the five-factor model to examine individual differences in symptom reporting. Again, the five factor model was used to examine individual personality characteristics, symptom reporting

and the type of symptom reported. Given this is a widely used measure of personality in a non-pathological population, the implications for use in a medical context to influence health outcomes should be considered.

As noted, previous research revealed the personality facet of Openness appeared to play an important role in both symptom reporting and the type of symptom reported (Baker, Kelly, and Kauffman 2010). There was no discernible pattern of reported symptoms associated with "medication" use and the overall Openness trait in the current study; however, the separate facets did seem to play a role. Participants reporting at least one symptom had significantly higher scores in two facets related to Openness, action and aesthetics. The same two facets were also related to placebo symptoms.

Personality characteristics such as pessimism and neuroticism have long been thought to influence overall health. Myers and Hwang (2002) pose the idea that neuroticism does indeed influence health by increasing psychological vulnerabilities such as nervous tension and anxiety. Disease and illness are thought to also influence neurotic symptoms such as anxiety while taxing the homeostatic balance of the body, thus again increasing psychological vulnerabilities and decreasing overall health. While the NEO-PI-3 examines neuroticism as a whole, the facets are often considered as a stand-alone quality or trait of an individual. Facets such as anxiety or depression are typically aligned with psychological disorders.

Using the present design of symptom reporting and personality domains, individuals scoring high in neuroticism tended to report higher negative symptoms associated with the pseudo medication. Given the difference between the number of positive symptoms reported (sixty-three percent of responses), and the number of negative symptoms (forty-eight percent of responses) the correlation existing between nocebo symptoms and a personality characteristic is

important. Of equally important note, individuals reporting anxiety as a personality trait also reported more overall symptoms. This finding better aligns with typical assumptions of an anxious individual's experience of somatic symptoms.

With respect to the facets of neuroticism and the type of symptom reported, multiple facets of Neuroticism influenced negative outcomes associated with the medication or side effects. Anxiety was found to be related to mild gastrointestinal disturbances. Participants reporting experiencing a headache as a side effect also reported increased in impulsivity and depression. Depression was also related to fatigue in the present study. Neuroticism as a personality characteristic was related to experiencing headaches and fatigue. These findings may also relate to the fact that people with psychological disorders tend to utilize health services at a higher rate (Simon, Khandker, Ichikawa, and Operskalski, 2006). Individuals who are anxious or depressed are likely to have a more negative outlook on their health and a higher sensitivity to somatic symptoms, real or perceived.

The overall communication of side effects or symptoms is likely mediated by the interpersonal relationship patients develop with their medical provider. The present research was carried out in a medical environment, the UNT Student Health and Wellness Center. It is hypothesized that this environment added to the expectancy often associated with medical treatments and trust in medical treatments. As noted earlier, the context in which placebo belief occurs has been identified as playing a key role in the amount and type of placebo responses (Benedetti, 2002). In the current study, individuals who reported a higher level of trust in both medical professionals and medical research had a higher number of reported symptoms.

The relationship between symptom reporting and a high level of trust in the medical field appears to support the idea that trust is both an intrinsic and instrumental part of medical

treatment. Trust occurs in medical trials as noted by Glasser and Frishman (2010). No matter the risk of side effects, patients will engage in a treatment based on trust of the physician. These findings also may shed light on the relationship of patient trust and its influence on medical treatment and overall outcomes. Medication has an influence over illness reduction and disease progression. In the current examination, trust in both the medical profession and trust in medical research appeared to influence the effects of *an inert capsule* disguised as a medication. Trust in both the medical profession and medical research appeared to influence total symptom reporting, as well as the total amount of favorable symptoms and specific symptom type. Participants did indeed report more physical symptoms and were more likely to report positive effects associated with the" medication" such as the ability to think more clearly. So trust certainly may influence the perceived efficacy of a true medication as well.

Trust in the medical profession and trust in medical research are assumed to share the same intrinsic qualities with trust as measured by the NEO-PI 3. The facet of trust as measured by the NEO-PI 3 was found to have no relationship with symptom reporting. So trust measured as an intrinsic value did not correlate with symptom reporting. Trust thought to have an instrumental component, as measured by the two trust questionnaires used in the experimental design, did share a relationship with symptom reporting. These findings support the idea that trust does indeed have an instrumental component. Furthermore, trust in the medical profession may be present in individuals who are not intrinsically trusting.

Understanding individual differences including trust only serves to build both treatment adherence and rapport regardless of treatment setting. It is unfortunate that there were not enough participants in the group that received "random" information concerning capsule content and reported believing they'd received the "medication", as opposed to those specifically told

they'd received the "medication". The importance of trust in that situation would have been very interesting. In any event, the present data does shed light into possible personality characteristics of placebo reactors and the fact that trust does play a role in a placebo reactors report of symptoms. The present study also highlighted symptom reporting in both the amount and type. Identifying a relationship between personality and symptom reporting and personality and symptom type may have implications in both the field of psychology and medicine.

It would be interesting to collect information concerning potential "side effect" responses without an information sheet describing typical experiences noted upon receiving the active substance. This would help elucidate into the relationship between personality domains without the influence of symptom expectancy. For example, future placebo/nocebo research aimed at identifying a placebo reactor might include control groups that receive no information about possible symptoms of a "treatment", and/or no "treatment", to allow for comparison to the experimental group that did receive such information (Johansen, Brox, & Flaten, 2003; Stewart-Williams, 2004). This comparison of an informed placebo control group to an uninformed placebo group may allow for a clearer identification of the true placebo effect with respect to placebo responses and a possible placebo reactor.

A weakness of the present design is the assumption that the participant viewed researcher as a medical provider. The context of a medical setting was used to improve the likelihood such a belief would occur, and in fact positive results were noted. It would be interesting to determine if further differences were noted using the participant's actual medical provider.

Results from the current study potentially have applications in both medicine and how we measure treatment effectiveness. Individual factors responsible for placebo responses are not often considered. In clinical trials for a medication, medication effectiveness is judged relevant a

to placebo group. As noted in many studies, especially those examining antidepressants, this is often difficult to achieve (Linde et al. 2007). Individual variables such as the type or amount of trust, or personality may affect both the number and the type of placebo/nocebo responses experienced by an individual. If in clinical trials possible placebo reactors could be identified based on levels of trust or personality characteristics it might lead to more accurate results.

More research is needed to understand placebo responses, the placebo reactor and overall symptom reporting. The present study demonstrated that personality characteristics, as a measure of individual differences, influence beliefs about medication efficacy and the type symptoms experienced. It further shed light on the fact that instrumental, not intrinsic trust may be more important in medicine and medical research. The nature of this interaction is still not fully understood, but is undoubtedly present and may account for as many treatment effects as the active treatment.

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