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A positive relationship between harm avoidance and brain nicotinic acetylcholine receptor availability

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ABSTRACT

Prior research indicates that disturbance of cholinergic neurotransmission reduces anxiety, leading to the hypothesis that people with heightened cholinergic function have a greater tendency toward anxiety-like and/or harm-avoidant behavior. We sought to determine if people with elevated levels of harm avoidance (HA), a dimension of temperament from the Temperament and Character Inventory (TCI), have high α4β2* nicotinic acetylcholine receptor (nAChR) availability. Healthy adults ($n=105$; 47 non-smokers and 58 smokers) underwent bolus-plus-continuous infusion positron emission tomography (PET) scanning using the radiotracer 2-[18F]fluoro-3-(2(S)azetidinylmethoxy) pyridine (abbreviated as 2-FA). During the uptake period of 2-FA, participants completed the TCI. The central study analysis revealed a significant association between total HA and mean nAChR availability, with higher total HA scores being linked with greater nAChR availability. In examining HA subscales, both 'Fear of Uncertainty' and 'Fatigability' were significant, based on higher levels of these characteristics being associated with greater nAChR availabilities. This study adds to a growing body of knowledge concerning the biological basis of personality and may prove useful in understanding the pathophysiology of psychiatric disorders (such as anxiety disorders) that have similar characteristics to HA. Study findings may indicate that heightened cholinergic neurotransmission is associated with increased anxiety-like traits.

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1. Introduction

Biopsychosocial theories of personality propose that certain facets of temperament are linked to neurobiological (and genetic) markers (Cloninger, 1986, 1987). Personality dimensions influence both affective (Canli et al., 2001) and cognitive (Kumari et al., 2004) function as well as the risk of psychiatric disorders (Elovainio et al., 2004; Bora and Veznedaroglu, 2007; Smith et al., 2008), highlighting the importance of characterizing the biological basis of personality. Towards the end of the twentieth century, Robert Cloninger developed and presented the Temperament and Character Inventory, based on a psychobiological model of personality that describes the structure and diversity of personality characteristics using four dimensions of temperament (novelty seeking, harm avoidance [HA], reward dependence, and persistence) and three dimensions of character (cooperativeness, self-directedness, and self-transcendence) (Cloninger et al., 1993). The four dimensions of temperament are thought to be genetically and biologically determined and stable over time (Cloninger and Svrakic, 1997). Respectively, the four dimensions of temperament describe an individual's propensity to pursue novelty, restrict behavior to avoid punishment, perform reward-related behaviors, and continue a behavior without reward. HA consists of the following subcharacteristics: anticipatory worry, fear of uncertainty, shyness, and rapid fatigability. Individuals rating high in HA tend to be pessimistic, cautious, and apprehensive (Cloninger et al., 1993; Pud et al., 2004), and HA is considered the most relevant of the four temperament dimensions to anxiety and affective disorders (Ampollini et al., 1999; Ball et al., 2002; Jiang et al., 2003).

Recently, increasing evidence implicates brain cholinergic neurotransmission in the modulation of harm-avoidant and anxiety-like behavior (Brioni et al., 1993; File et al., 2000; Newman et al., 2001). Neuronal nicotinic acetylcholine receptor (nAChR) antagonists such as mecamylamine (Newman et al., 2001, 2002; Lippiello et al., 2008; Zarrindast et al., 2008; Roni and Rahman, 2011), lobeline (Roni and Rahman, 2011), and methyllycaconitine (Tucci et al., 2003b) produce anxiolytic effects in animal models of anxiety. Furthermore, recent animal studies have demonstrated that partial and full agonists at nAChRs result in anxiolytic effects, suggesting that disturbance of brain cholinergic neurotransmission results in these effects (Brioni et al.,

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1993, 1994; Arneric et al., 1994; Decker et al., 1994; Skoubis et al., 2006; Feuerbach et al., 2009; Turner et al., 2010). In addition, nicotine, acting as an agonist at nAChRs, can generate both anxiogenic and anxiolytic effects in animals (File et al., 1998; Ouagazzal et al., 1999; Picciotto et al., 2002; Graef et al., 2011) and humans (Picciotto et al., 2002; Tucci et al., 2003a; Graef et al., 2011; Kobiella et al., 2011) depending on the circumstance. Nicotine's effects on anxiety behavior are influenced by dose, route of administration, acute or chronic dosing, time of testing, genetic background of animal subjects, and behavioral status (Picciotto et al., 2002). Taken together, this prior research indicates that disturbance of the cholinergic system may reduce anxiety, leading to the hypothesis that people with heightened cholinergic neurotransmission may have a greater tendency toward anxiety-like or harm-avoidant behavior.

Within the cholinergic system, the α4β2* nAChR subtype is one of the most abundant in the mammalian brain (Wu et al., 2006), and has been specifically linked with anxiety in animal models. In one such study, inactivation of β2*-containing nAChRs with a specific receptor antagonist reduced fear-like and anxiety-like behavior in rodents (Anderson and Brunzell, 2012). Similarly, β2*-containing nAChRs have been shown to be critical for the nicotine-induced enhancement of contextual fear conditioning (Wehner et al., 2004; Davis et al., 2007) and to mediate the anxiety-like and affective components of nicotine withdrawal (Jackson et al., 2008). In addition, α4-containing nAChRs have been shown to be necessary for the anxiolytic effects of nicotine (McGranahan et al., 2011). And, in a study of humans with major depressive disorder, both positive and negative associations were reported between β2*-containing nAChR availability and trait anxiety across a group of regions that differed from the ones studied here (Saricicek et al., 2012). Thus, these studies generally link the common α4β2* nAChR subtype with the mediation of anxiety-like or harm-avoidant behaviors.

Brain imaging studies of the dopaminergic, serotonergic, and opioid neurotransmitter systems have also examined links with HA. For dopaminergic neurotransmission, HA has been associated with high dopamine turnover (Kaasinen et al., 2001) and low dopamine receptor (D2/3) availability (Kim et al., 2011; Yasuno et al., 2001). For serotonergic neurotransmission, HA was found (in women) to be associated with increased 5-HT2A receptor binding potential (Bailer et al., 2004), and recent research has shown that serotonergic neurons in the dorsal raphe nucleus contain functional postsynaptic nAChRs, providing a mechanism by which the serotonergic system may influence nAChR density (Commons, 2008; Galindo-Charles et al., 2008). And for opioid neurotransmission, high HA score was shown to be associated with high μ-opioid receptor availability (implying low endogenous μ-opioid drive) (Tuominen et al., 2012). Taken together, these pioneering studies implicate high dopaminergic and low serotonergic and opioid neurotransmission in research participants with high HA. While dopaminergic, serotonergic, and opioid neurotransmission have begun to be characterized in relation to the personality trait HA, cholinergic neurotransmission has not yet (to our knowledge) been examined with brain imaging studies of humans.

Thus, we undertook a study to advance the characterization of the neuroreceptor profile of HA in a relatively large sample of healthy control participants. In the study presented here, we examined the relationship between HA and α4β2* nAChR availability in previously defined regions of interest (thalamus, cerebellum, brainstem, and prefrontal cortex) using high resolution positron emission tomography (PET) scanning.

2. Methods

2.1. Participants and screening methods

One hundred and five otherwise healthy adults (47 non-smokers and 58 smokers) completed the study and had usable data. Utilizing the same inclusion/exclusion criteria as in our previous reports (Brody et al., 2011, in press), participants were recruited and screened, and the study sample here was a subset of the group used in a previous report by our group comparing smokers and non-smokers (Brody et al., 2013). For non-smokers, the central inclusion criterion was absence of cigarette smoking for at least the past year. For cigarette smokers, the central inclusion criteria were smoking 10–40 cigarettes per day and current nicotine dependence. Exclusion criteria for all study participants included: any history of substance abuse/dependence or mental illness, history of a medical condition or use of a medication that could affect central nervous system functioning during scanning, or pregnancy. Screening questions from the SCID-IV (First et al., 1995) were asked to participants, in order to rule out any history of substance abuse/dependence (other than nicotine dependence) and mental illness.

During an initial study visit, screening information was obtained to characterize smoking and other past history. Rating scales administered were: the Fagerström Test for Nicotine Dependence (FTND) (Fagerstrom, 1978; Heatherton et al., 1991), the Smoker's Profile Form (including a detailed smoking history and demographic variables), the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1969), and the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967). To confirm smoking status, an exhaled carbon monoxide (CO) level was measured using a MicroSmokerlyzer (Bedfont Scientific Ltd, Kent, UK), with a CO ≥ 8 ppm (ppm) considered consistent with active smoking status and a CO of ≤ 4 ppm being considered consistent with non-smoking status. A urine toxicology screen (Test Country I-Cup Urine Toxicology Kit), breathalyzer test (AlcoMatePro), and urine pregnancy test (for female participants of reproductive potential) (Test Country Cassette Urine Pregnancy Test) were obtained at the screening visit to verify the participant's report of no current drug or alcohol dependence and no pregnancy. The local institutional review board (IRB) approved this study, and participants gave written informed consent.

2.2. Abstinence period and positron emission tomography (PET) protocol

Approximately 1 week after the initial screening session, participants underwent PET scanning adhering to the same general procedure as in our previous reports (Brody et al., 2009, 2011, 2013). Smoker group participants began nicotine/smoking abstinence two nights before each PET session and were monitored as previously described (Brody et al., 2009, 2011). In this way, we attempted to minimize the effects of nicotine from smoking on PET radiotracer binding during scanning.

At 11 AM on the day of scanning, study participants came to the VA Greater Los Angeles Healthcare System, and nicotine/smoking abstinence was confirmed by participant report and an exhaled CO ≤ 4 ppm. At 11:45 AM, each participant had an intravenous line placed in a room next to the PET scanner. Bolus-plus-continuous-infusion of 2-FA was started at 12 PM. The volume of 2-FA given as a bolus was equal to the volume infused over 500 min ($K_{bolus}=500$ min) (Kimes et al., 2008). This K_{bolus} effectively reached an approximate steady state in past studies by our group and others (Kimes et al., 2008; Brody et al., 2009, 2011). After the bolus-plus-continuous-infusion was initiated, participants remained seated in the room next to the PET scanner for the next 4 h, allowing the radiotracer to come to a relatively steady state in the brain. At 4 PM, PET scanning began and proceeded for 3 h, with a 10-min break following the first 90-min. Scans were obtained as series of 10-min frames.

PET scans were acquired with the Philips Gemini TruFlight (Koninklijke Philips Electronics N.V., Eindhoven, the Netherlands), a fully 3-dimensional PET-CT scanner, which was operated in non-TOF mode. Reconstruction was performed using Fourier rebinning and filtered back projection, and scatter and random corrections were applied. The mean spatial resolution (FWHM) for brain scanning is 5.0 mm (transverse) by 4.8 mm (axial). 2-FA was prepared using a published method (Dolle et al., 1998). Participants received a magnetic resonance imaging (MRI) scan of the brain within 1 week of PET scanning with the same specifications to those in our previous report (Brody et al., in press).

During PET scanning, 5 mL blood samples were drawn to determine free, unmetabolized 2-FA and nicotine levels in plasma. For 2-FA levels, 4 samples were drawn as standards before 2-FA administration and 9 samples were drawn during PET scanning at predetermined intervals. 2-FA levels were measured using previously published methods (Shumway et al., 2007; Sorger et al., 2007). For nicotine levels, blood samples were obtained before and after PET scanning. After the samples were centrifuged, they were sent to Dr. Peyton Jacob's laboratory at UCSF, where venous plasma nicotine concentrations were determined using an adapted version of a published GC–MS method (Jacob et al., 1991). The lower limit of quantification for this method was 0.2 ng/mL. In addition to the participants described in this paper, 19 smokers completed study procedures but were not included in the data analysis, as their plasma nicotine concentrations were unacceptably high ($>$ 0.4 ng/mL) (determined after study participation).

2.3. Symptom rating scale administration

In addition to baseline rating scales cited above, the Temperament and Character Inventory was administered once during the 2-FA uptake period (Cloninger et al., 1993), taking approximately 1–2 h to complete.