Title

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Journal

Psychiatry Research, 214(3)

ISSN

0165-1781

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Publication Date

2013-12-01

DOI

10.1016/j.pscychresns.2013.07.010

Peer reviewed

Psychiatry Research: Neuroimaging 214 (2013) 415–421

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

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

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ARTICLE INFO

Article history:
Received 18 November 2012
Received in revised form
22 June 2013
Accepted 25 July 2013

Keywords:
Harm avoidance
Temperament and Character Inventory
Tobacco
Nicotine dependence
Positron emission tomography
Nicotinic acetylcholine receptor

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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0925-4927/$ - see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.pscychresns.2013.07.010

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.

2.4. PET image analysis

After motion and decay correction, participants' PET scans were co-registered to their MRI images using PMOD version 2.9. Regions of interest (ROIs) were drawn on MRI using PMOD and transferred to the co-registered PET scans. ROIs were the thalamus, brainstem, cerebellum, and prefrontal cortex (PFC), which were chosen based on previous reports demonstrating a range of 2-FA receptor binding in these areas, while having at least moderate nAChR availability (Brody et al., 2006; Kimes et al., 2008; Mukhin et al., 2008). Mean V_T/f_P was used here for data analysis in order to limit Type I error, given that this study included a rating scale with 4 subscales and 4 ROIs, and because smokers have been consistently shown to have similar nAChR changes in almost all brain regions studied (Staley et al., 2006; Mamede et al., 2007; Mukhin et al., 2008; Wullner et al., 2008; Brody et al., 2013). The thalamus, cerebellum, and brainstem were drawn as whole structures, while representative slices of the PFC were drawn. ROI placement was visually examined for each PET frame to minimize effects of movement and co-registration errors. If a noticeable problem was detected, this procedure was repeated.

Total volume of distribution (expressed as V_T/f_P, based on established nomenclature (Innis et al., 2007)) was determined for each region and used as a measure of nAChR availability for the central study analyses. V_T/f_P values were calculated from the seventeen 10-min PET frames as the ratio $C_T/(C_P f_P)$, where C_T is the total concentration of 2-FA in the ROIs, f_P is the fraction of free (not protein bound) 2-FA in plasma, and $(C_P f_P)$ is the concentration of free 2-FA in plasma. The fraction of unmetabolized free (unbound) 2-FA was similar for the nonsmoker and smoker groups.

2.5. Statistical analysis

For descriptive demographic variables, means (± standard deviations) of these data were determined. For the central study analysis, a univariate analysis of covariance (ANCOVA) was performed, with mean V_T/f_P values averaged across the 4 ROIs as the dependent variable, smoking status (smoker versus nonsmoker) as a fixed factor (because smoking is known to up-regulate nAChR levels across almost all brain regions studied), and total harm avoidance score as a covariate of interest. To clarify the significant finding from the preceding analysis, ANCOVAs were performed with the same variables using subscales of the overall harm avoidance scale as covariates of interest instead of total HA scores. For completeness, *post hoc* linear regression was performed within the smoker and non-smoker groups with mean V_T/f_P value as the dependent variable and total HA (and subscales) as independent variables, in order to clarify whether smoking status impacted the significant overall findings.

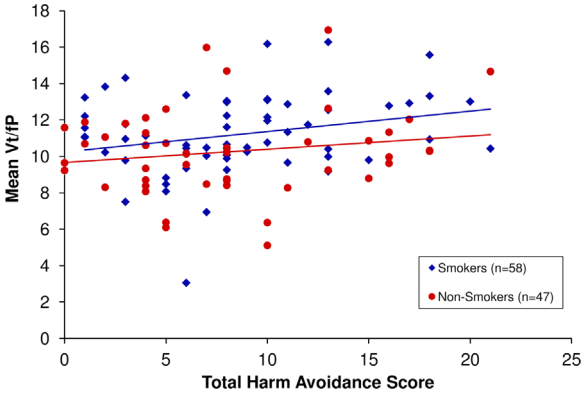

Fig. 1. Significant association between mean V_T/f_P (a marker for α4β2*availability) and total Harm Avoidance scores (ANCOVA; d.f.=1, 101; F=4.7; P=0.03). Similar results were found for the smoker and non-smoker subgroups.

3. Results

The study sample was middle-aged (38.1 ± 12.8 years old), 60% male, and was representative of the west Los Angeles area in terms of race/ethnicity (54 Caucasians, 26 African-American, 10 Hispanic, and 15 Asian or Mixed). The sample had a mean 14.7 ± 2.1 years of education, drank 2.3 ± 3.3 alcoholic beverages per week, and drank 1.3 ± 1.5 coffee cup equivalents of caffeine per day. The sample had a mean total HA score of 8.4 ± 5.3 and minimal anxiety and depressive symptoms (HAM-A and HAM-D scores of 2.1 ± 2.3 and 1.8 ± 2.1, respectively). Eleven participants reported occasional marijuana use (≤ 2 uses per week). The smokers and non-smokers did not differ significantly in demographic or rating scale variables (Table 1). Consistent with prior research (Etter et al., 2003, 2010), smokers had slightly, but non-significantly (unpaired t test), higher total HA scores than non-smokers (total and subscale scores of 8.7 ± 5.1, 2.3 ± 1.8, 2.4 ± 1.6, 1.8 ± 1.9, and 2.1 ± 2.0 for smokers and 8.1 ± 5.5, 2.2 ± 1.8, 2.6 ± 1.7, 1.9 ± 2.1, and 1.4 ± 1.6 for non-smokers).

The central study analysis revealed a significant association between mean V_T/f_P values and total HA score (ANCOVA; d.f.=1, 101; F=4.7; P=0.03), with higher V_T/f_P values being associated with greater total HA scores (Figs. 1 and 2). This analysis also revealed the expected main effect of smoking status (ANCOVA; d.f.=1, 101; F=4.6; P=0.04), with smokers having higher mean V_T/f_P values than non-smokers, presumably due to α4β2* nAChR up-regulation (Benwell et al., 1988; Breese et al., 1997). For this ANCOVA, the effect size (η^2) was 0.088 of which 0.044 was from HA and 0.043 from smoking status.

As for the HA subscales, both 'Fear of Uncertainty' (ANCOVA; d.f.=1, 101; F=7.9; P=0.006) and 'Fatigability' (ANCOVA; d.f.=1, 101; F=4.6; P=0.03) were significant, with increasing V_T/f_P values being associated with higher levels of these measures. The other two subscales of HA ('Anticipatory Worry' and 'Shyness') did not have significant associations with nAChR availability (F's=1.2 and 0.2, respectively).

As for the subgroups of participants based on smoking status (smokers and non-smokers), these subgroups had similar directional relationships between V_T/f_P values and total HA (linear regression, P=0.06 and P=0.25, respectively), indicating that the overall result for total HA was similar for both smokers and non-smokers (Fig. 1). Likewise, linear regression demonstrated that both subgroups also contributed to the significant findings for the HA subscales ('Fear of Uncertainty': P=0.01 for smokers and P=0.15 for non-smokers; 'Fatigability': P=0.35 for smokers and P=0.02 for non-smokers), indicating that the relationship between HA and nAChR availability was not dependent on smoking status.

Table 1
Demographic and rating scale variables for the overall study sample and subgroups based on smoking status.

Variable	Study sample (n=105)	Smoker subgroup (n=58)	Non-smoker subgroup (n=47)
Age	38.1 (± 12.8)	38.7 (± 13.4)	37.4 (± 12.1)
Gender (% female)	40	36	45
Ethnicity (% Caucasian)	51	48	55
Education (years)	14.7 (± 2.1)	14.4 (± 2.1)	15.1 (± 2.1)
Cigarettes per day	N/A	18.7 (± 4.2)	N/A
Caffeine (coffee cup equivalents) per day	1.3 (± 1.5)	1.6 (± 1.6)	1.0 (± 1.3)
Alcoholic Beverages per week	2.3 (± 3.3)	2.8 (± 4.1)	1.7 (± 2.0)
HAM-A Rating Scale Score	2.1 (± 2.3)	2.2 (± 2.4)	2.0 (± 2.2)
HAM-D Rating Scale Score	1.8 (± 2.1)	2.0 (± 2.2)	1.6 (± 2.0)

The smoker and non-smoker subgroups did not differ significantly in any of the variables listed (unpaired t or chi-square tests nonsignificant) other than cigarettes per day. HAM-A=Hamilton Anxiety Rating Scale. HAM-D=Hamilton Depression Rating Scale.

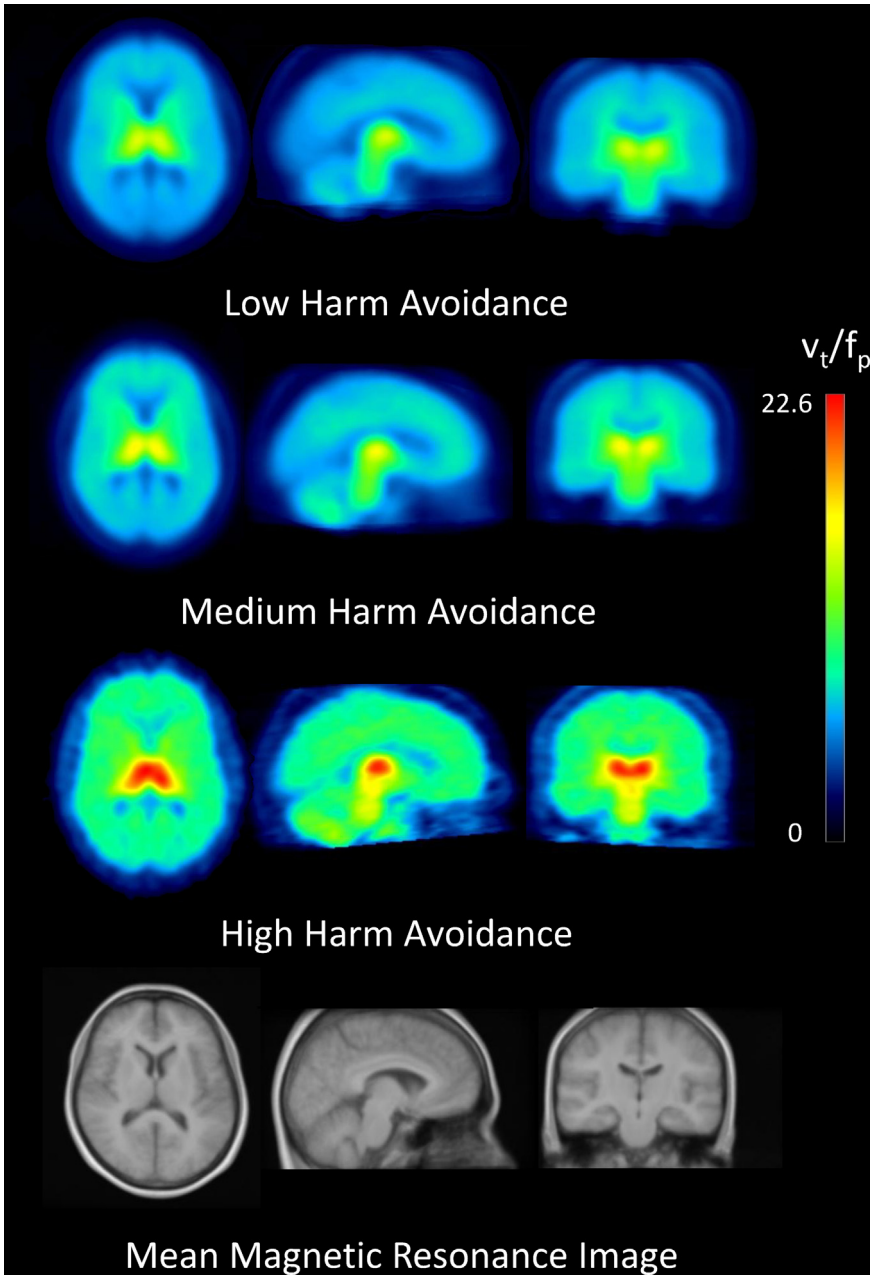

Fig. 2. Mean positron emission tomography (PET) images from study subgroups based on total Harm Avoidance (HA) scores, showing transaxial, saggital, and coronal views (columns 1–3). Top row shows the low HA group (range of scores 0–6; mean – 3.6), 2nd row shows medium HA (range of scores 7–9; mean – 7.9), and 3rd row show high HA (range of scores 10–25; mean – 14.0). Bottom row shows a mean magnetic resonance image of study participants.

4. Discussion

Study results demonstrate a positive association between mean nAChR availability in pre-defined ROIs (thalamus, cerebellum, brainstem, and PFC) and total scores for the personality trait Harm Avoidance. Two of the HA subscales ('Fear of Uncertainty' and 'Fatigability') were positively associated with mean nAChR availability, while one subscale ('Anticipatory Worry') had a non-significant positive association and the other subscale ('Shyness') had no association. The present study adds to a growing body of knowledge concerning the biological basis of personality. While we are not aware of brain imaging studies linking HA with nAChR availability, a prior behavioral genetics study found links between single nucleotide polymorphisms within the nAChR α4 subunit gene (CHRNA4) and HA (Roe et al., 2009), providing additional evidence for the mediation of HA by the cholinergic system. Furthermore, the findings here are consistent with prior research which demonstrates that the cholinergic system is linked with potentiation of a broad range of adaptive behaviors to environmental stimuli (Picciotto et al., 2012), which includes nAChR mediation of fear-like responses (Davis and Gould, 2007; Anderson and Brunzell, 2012), and also includes influences on attention, food intake, and affect.

In addition to cholinergic neurotransmission, previous studies have shown negative correlations between HA scores and dopamine D2/3 receptor availability in the pre-commissural dorsal caudate and post-commissural putamen (Kim et al., 2011), serotonin 5-HT (2) receptor availability in the frontal and left parietal cortex (Moresco et al., 2002), and serotonin transporter availability in the brainstem (Wu et al., 2010). In relation to the present study, these findings suggest that heightened cholinergic neurotransmission is associated with increased intrasynaptic dopamine and serotonin and diminished receptor availabilities. This theory is supported by

previous studies demonstrating nicotine-induced dopamine release in the ventral striatum/nucleus accumbens using microdialysis (Di Chiara and Imperato, 1988; Damsma et al., 1989; Pontieri et al., 1996; Sziraki et al., 2001). Along these same lines, nicotine-induced dopamine release is inhibited when dopaminergic neurons are lesioned prior to nicotine administration (Corrigall et al., 1992). With respect to serotonergic neurotransmission, recent research has demonstrated that serotonergic neurons in the dorsal raphe nucleus possess functional postsynaptic nAChRs, providing a mechanism by which brain cholinergic neurotransmission may influence serotonin neurotransmission (Commons, 2008; Galindo-Charles et al., 2008).

Our results also support existing research implicating the thalamus, cerebellum, and PFC (regions specifically examined here) in the modulation of harm-avoidant behavior. Hakamata et al. (2006) reported a positive correlation with the level of glucose metabolism in the right medial dorsal thalamic nucleus, a region thought to modify emotion and mood. Additionally, O'Gorman et al. (2006) discovered a strong negative correlation between HA and perfusion in the cerebellar vermis. Several studies have examined the role of the PFC in HA, and findings have included a negative correlation between HA and gray matter volume in the left PFC (Van Schuerbeek et al., 2011) and negative correlations between HA and glucose metabolism in the anterior ventromedial PFC (Hakamata et al., 2009) and left anterior PFC (Yamasue et al., 2008) in females. Furthermore, prior research has demonstrated significant activation of the dorsomedial PFC during internally driven uncertainty (Zaretsky et al., 2010) and right dorsolateral PFC during the anticipation of aversive stimuli (Nitschke et al., 2006), thereby linking PFC function with HA.

This study had several limitations. While the study size was substantial for a brain imaging study of this type, an even larger sample size would be needed to verify whether the smoker and non-smoker subgroups indeed had similar relationships between brain nAChR availability and HA, since these subgroup results were slightly different and it cannot be definitively concluded that the subgroups had the same relationship between nAChR availability and HA. Also, it should be noted that the Temperament and Character Inventory was administered during the 2-FA uptake period after 2 days of nicotine abstinence, and this timing may have had an unintended effect on the results from the smoker group given that their responses were collected in the setting of acute nicotine withdrawal. Furthermore, while we found a relationship between higher nAChR availability and higher HA, the causal relationship between nAChR availability and HA levels is unclear. And, while the TCI is a commonly-used, well-validated rating scale, the use of other personality rating scales, such as the NEO Personality Inventory-3 (NEO-PI-3), would have been helpful to confirm study results (McCrae et al., 2005).

Results of this study suggest that HA is associated with nAChR availability across brain regions and provide further evidence supporting a biological basis of personality. As personality dimensions influence the risk of psychiatric disorders, knowledge of biological and genetic determinants of personality may prove useful in understanding the pathophysiology of these conditions, and may (in the future) guide the development of new treatments for such disorders.

Acknowledgements

This study was supported by the Tobacco-Related Disease Research Program (A.L.B. [19XT-0135]), the National Institute on Drug Abuse (A.L.B. [R01 DA20872]), and the Department of Veterans Affairs (Merit Review Award [A.L.B.]). The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The authors report no biomedical financial disclosures or potential conflicts of interest.

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