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Displacement behaviors in chimpanzees (*Pan troglodytes*): A neurogenomics investigation of the RDoC Negative Valence Systems domain

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Abstract

The current study aimed to systematically investigate genetic and neuroanatomical correlates of individual variation in scratching behaviors, a well-validated animal-behavioral indicator of negative emotional states with clear links to the NIMH Research Domain Criteria (RDoC) response to potential harm ("anxiety") construct within the Negative Valence Systems domain. Utilizing data from a sample of 76 captive chimpanzees (*Pan troglodytes*), we (a) examined the association between scratching and presence or absence of the RS3-containing DupB element in the *AVPR1A* 5' flanking region, (b) utilized voxel-based morphometry (VBM) to identify gray matter (GM) voxel clusters that differentiated *AVPR1A* genotype, and (c) conducted a VBM-guided voxel-of-interest analysis to examine the association between GM intensity and scratching. *AVPR1A* evidenced sexually dimorphic associations with scratching. VBM analyses revealed significant differences in GM by genotype across twelve clusters largely in the frontal cortex. Regions differentiating *AVPR1A* genotype showed sex-specific associations with scratching. Results suggest that sexually dimorphic associations between *AVPR1A* and scratching may be explained by genotype-specific neuroanatomical variation. The current study provides an example of the way in which chimpanzee research is uniquely poised for multilevel, systematic investigations of psychopathology-relevant constructs within the context of the RDoC framework.

Descriptors: Displacement behaviors, AVPR1A, Voxel-based morphometry, RDoC, Negative Valence Systems, Chimpanzees

The National Institute of Mental Health (NIMH) recently launched the Research Domain Criteria (RDoC; Cuthbert & Insel, 2013; **Kozak & Cuthbert, 2016**; Insel et al., 2010) initiative, which aims to elucidate the neurobiological basis of mental illness. This initiative has explicitly challenged researchers to consider mental illness from a dimensional, transdiagnostic perspective, a direct contrast to the *Diagnostic and Statistical Manual*'s (DSM; APA, 2013) manifest polythetic dichotomous approach to categorizing mental disorders. Specifically, RDoC represents an attempt to progress toward new conceptions of psychopathology based around an understanding of the neurobiological basis of behavior. Approached in this way, the RDoC matrix is intended to provide a framework for psychopathology research. Specifically, the matrix includes five broad domains (e.g., Negative Valence Systems, Systems for Social Processes), each of which includes several lower-order constructs (e.g., response to potential harm), to be investigated in terms of various units of analysis (e.g., genes, physiology, behavior). Consistent with the RDoC initiative, investigations of behavioral variation in these domains across various units of analysis can explicitly inform our understanding of the various forms of psychopathology associated with these domains (i.e., a transdiagnostic approach).

Based within the RDoC framework, the current study describes the way in which studies in chimpanzees (*Pan troglodytes*) can be used to investigate the RDoC Negative Valence Systems (NVS) domain. Specifically, we systematically investigated genetic and neuroanatomical correlates of individual variation in scratching behaviors, a widely studied, well-validated intermediate behavioral

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phenotype with clear links to the response to potential harm ("anxiety") construct within the NVS domain. The RDoC initiative explicitly encourages investigators to utilize animal models to investigate constructs within the various specified domains. Chimpanzees are particularly well suited as an animal model for the examination of these constructs including constructs within the NVS domain. Indeed, in addition to an extremely high percentage of shared genes, it is now widely accepted that humans and chimpanzees share many emotional processes, providing the foundation for an unparalleled animal model of human emotion (de Waal, 1996; Phillips et al., 2014). Thus, chimpanzee models provide a unique means to investigate highly complex processes associated with basic phenotypic traits such as those in the NVS domain, largely free from the typical sociocultural confounds inherent in human studies (Nelson & Winslow, 2009). A comparative approach using chimpanzees therefore allows for a relatively straightforward analysis of biological processes contributing to the NVS domain.

Scratching Behaviors as an Indicator of Negative Arousal

In primates, self-directed displacement activities such as scratching have been consistently found in the context of negative emotional states including stress, anxiety, and frustration (Aureli & Whiten, 2003; Maestripieri, Schino, Aureli, & Troisi, 1992). As reviewed by Troisi (2002), in nonhuman primates, the most common displacement activities are comfort behaviors focused on body care (i.e., scratching). These behaviors look quite similar in humans, often taking the form of self-grooming behaviors such as head scratching or beard stroking (Troisi, 1999). Among nonhuman primates, a large literature suggests that self-directed behaviors such as scratching operate as an indicator of anxiety related to uncertainty, social tension, or impending danger (for a comprehensive review, see Aureli & Whiten, 2003). For example, research with both captive macaques (Pavani, Maestripieri, Schino, Turillazzi, & Schucchi, 1991; Troisi & Schino, 1987) and wild olive baboons (Castles, Whiten, & Aureli, 1999) has found higher rates of self-scratching when an individual is closer in proximity to a higher-ranking monkey, a time when interindividual aggression is more likely, than when alone or near a subordinate monkey. Further, increased self-directed behaviors have been found in both long-tailed macaques (Aureli, 1992) and olive baboons (Castles & Whiten, 1998) in response to intragroup aggressions in both the victim and the aggressor until reconciliation occurs. Scratching has also been observed in capuchin monkeys in response to a stressful self-control task, particularly initially before subjects habituated to the task (Ventricelli et al., 2013). Among chimpanzees, impending risk of aggression as indicated by vocalizations from neighboring groups of captive chimpanzees has been found to be associated with increased rates of self-directed behaviors, most notably scratching (Baker & Aureli, 1996). Scratching has also been found to increase during difficult compared to easy cognitive behavioral tasks, particularly following incorrect responses (Leavens, Aureli, & Hopkins, 2004; Leavens, Aureli, Hopkins, & Hyatt, 2001). Further, and most relevant to the current study, increased rates of scratching have been found among chimpanzees in response to videos of scenes depicting affiliative and agonistic encounters between chimpanzees with accompanying vocalizations (Hopkins et al., 2006).

Further evidence of the link between scratching and negative arousal comes from pharmacological studies involving anxiolytic and anxiogenic drugs. For example, among long-tailed macaques, Shino, Perretta, Taglioni, Monaco, and Troisi (1996) found that administration of lorazepam, an anxiolytic, decreased rates of scratching whereas FG 7142, an anxiogenic, increased these behaviors in a dose-dependent manner. Taken together, results of experimental behavioral and pharmacological studies in primates clearly suggest that scratching behaviors are a valid indicator of the negative arousal associated with anxiety. Considered within the RDoC framework, this phenotype clearly links to the response to potential harm construct within the NVS domain.

Vasopressin V1a Receptor Gene (*AVPR1A*)

Vasopressin is a neuropeptide with multiple physiological functions that has been strongly implicated in the development and evolution of complex social behavior in mammals. Indeed, variations in the vasopressin system associated with a polymorphism in the promoter region of the vasopressin V1a receptor gene (*AVPR1A*) play a prominent role in producing diversity in social behavior across numerous species including humans and chimpanzees, particularly for males (Donaldson & Young, 2008; Ebstein, Knafo, Mankuta, Chew, & Lai, 2012; Hammock, Lim, Nair, & Young, 2005; Hammock & Young, 2005, 2006; Latzman, Hopkins, Keebaugh, & Young, 2014; Walum et al., 2008; Young & Wang, 2004). Many of these association studies focus on a polymorphic repetitive element known as RS3. In humans, the RS3 repeat region is housed within a larger, ~350 bp tandem duplicated region. The first of these duplicated regions, DupA, spans −3,730 to −4,074 bp relative to the transcription start site and contains a $GT_{20\text{-}26}$ microsatellite, known as STR1. The second block, DupB, spans −3,382 to −3,729 bp and contains the complex microsatellite, RS3 $[(CT)_{6\text{-}14}(GT)_{8\text{-}24}]$. Approximately 65% of the captive chimpanzees in previous studies have a complete deletion of the DupB region, leading to a 357 bp difference between the $DupB^+$ and Dup^- alleles. The deletion of RS3 in some individuals makes this species ideal for assessing the potential role of the *AVPR1A* gene, and more specifically RS3, on aspects of sociality including affiliation and social communication. This is particularly important in the context of the current study, which aimed to examine a behavioral indicator of stress or anxiety (i.e., scratching) in response to viewing of video scenes of other conspecifics in both affiliative and agonistic encounters. For instance, previous studies have shown that $DupB^+$ and $DupB^-$ chimpanzees differ significantly in the personality dimensions of dominance and conscientiousness (Latzman et al., 2014). Notably, male $DupB^+$ chimpanzees were found to have higher dominance scores than $DupB^-$ males while no difference was found in females. Based on these findings, to the extent that dominance status of an individual chimpanzee might influence behavioral reactivity in response to seeing and hearing the behavior and vocalizations of unfamiliar apes, one can certainly hypothesize that the RS3 polymorphism may mediate responses to these types of cues, including behaviors indicative of stress. Providing additional support for this hypothesis are rodent studies demonstrating the importance of this receptor in anxiety-like behaviors, including scratching, in male (Bielsky, Hu, Szegda, Westphal, & Young, 2004) but not female (Bielsky, Hu, & Young, 2005) mice.

Current Study

Consistent with an RDoC approach to examining constructs across multiple levels of analysis, the current study sought to examine the response to potential harm ("anxiety") construct within the RDoC NVS domain through a systematic neurogenomic investigation of

scratching behaviors induced by a mild social stressor in a sample of socially housed captive chimpanzees. The work was performed in three steps. First, we examined whether scratching behaviors were influenced by the presence or absence of the RS3-containing DupB element in the *AVPR1A* 5' flanking region. Next, to determine the brain regions that differentiate between $DupB^{-/-}$ and $DupB^{-/+}$ individuals, the association between *AVPR1A* genotype and variation in gray matter (GM) distribution in the brain was assessed using voxel-based morphometry (VBM). In human and nonhuman primates, there is relatively little data on genetic polymorphism in the *AVPR1A* gene and either neurofunctional or neuroanatomical organization of the brain (Meyer-Lindenberg et al, 2009; Zink & Meyer-Lindenberg, 2012; Zink, Stein, Kempf, Hakimi, & Meyer-Lindenberg, 2010). VBM has several advantages over more traditional region-of-interest (ROI) approaches for measuring neuroanatomical differences in GM. For example, VBM allows for a comparison of the local composition of GM while discounting positional and other large-scale volumetric differences in gross anatomy. Further, VBM minimizes problems associated with observer bias associated with manual tracing or other ROI techniques. All told, VBM offers a powerful approach for assessing neuroanatomical differences in GM between groups across the entire brain. Thus, we chose to employ VBM to investigate clusters of voxels that differentiated $DupB^{-/-}$ and $DupB^{-/+}$ individuals within this sample.

Finally, after determining areas of the brain in which GM intensity differed by *AVPR1A* genotype, a voxel-of-interest (VOI) analysis approach was used to examine associations between GM in these areas and scratching behaviors. Specifically, we identified GM clusters that distinguished $DupB^{+/-}$ and $DupB^{-/-}$ chimpanzees and converted them to object maps or masks. These masks were then applied to the individual GM volumes of the chimpanzees, and the intensity of GM within each cluster was quantified and subsequently correlated with individual variation in scratching behavior.

Given previous findings of sexually dimorphic associations between social behaviors including anxiety-related behaviors and *AVPR1A* (e.g., Beilsky et al., 2004; 2005; Donaldson & Young, 2008; Latzman et al., 2014; Winslow, Hastings, Carter, Harbaugh, & Insel, 1993), along with previous findings suggesting a higher expression of arginine vasopressin in males (e.g., Goodson & Bass, 2001), we expected to find sexually dimorphic variation in the *AVPR1A* in chimpanzees linked to individual variability in scratching behaviors. Further, after explicating areas of the brain that differentiated between $DupB^{-/-}$ and $DupB^{-/+}$ individuals, we expected that this sex-specific pattern would be evident in the associations between GM values in these regions and scratching behaviors.

Method

Subjects

Behavioral and genotype data were available in 76 captive chimpanzees including 31 males ($M_{age} = 17.94$, $SE = 1.99$) and 45 females ($M_{age} = 25.23$. $SE = 1.70$). All chimpanzees were members of the Yerkes National Primate Research Center (YNPRC) colony of apes. Chimpanzees were housed in social groups ranging from 2 to 16 individuals. The current sample included 45 chimpanzees (28 females, 17 males) with the $DupB^{-/-}$ and 31 individuals (17 females, 14 males) with the $DupB^{+/-}$ genotype.

All aspects of the research complied with the American Psychological Association's Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research (APA, 2012), followed the Institute of Medicine guidelines for research with chimpanzees, and was done with the approval of the local Institutional Care and Use Committees. The chimpanzees were housed in indoor-outdoor compounds and had access to both portions of their enclosures 24 h a day. During the winter seasons, the indoor facilities were heated, while air conditioning or fans and misters are provided in the hotter summer months. Lighting in the outdoor facility follows the typical seasonal cyclic change in sunrise and sunset. Standard tungsten lighting is provided in the indoor facility, and the lights are on a 12-h on/off cycle. The chimpanzees are fed two to five times per day with a diet that consists of fruits, vegetables, and commercially produced primate chow. In addition, they receive a number of foraging opportunities each day. Environmental enrichment, such as simulated tool use tasks or other non-nutritive substrates were provided to the chimpanzees on a daily basis. At no time were the subjects ever food or water deprived.

Displacement Behavior

As an indicator of the response to potential harm ("anxiety") construct, scratching behaviors were assessed. Specifically, as described previously (Hopkins et al., 2006), we measured scratching behavior under experimental and baseline conditions. To elicit scratching in response to social stimuli, video clips of unfamiliar chimpanzees were presented to the subjects. Video clips were filmed using a Canon ZR90 digital video camera at YNPRC. Clips were filmed of two separate chimpanzee social groups after receiving a watermelon. The video included scenes and accompanying vocalizations of chimpanzees in both affiliative and agonistic encounters as they negotiated possession and sharing of the watermelon. Clips were then captured and edited using Roxio Videowave Movie Creator for Windows. The 30-min video was then presented to the chimpanzees using a computer system and a 17-in computer monitor placed on a rolling cart.

Procedure

The exact details have been described previously in Hopkins et al. (2006). Briefly, frequencies in scratching bouts were recorded during two conditions. During the baseline condition, the experimenter located herself outside of the subject's home cage and recorded all bouts of scratching for a period of 30 min. The experimenter sat approximately 2.5 m from the mesh of either the inside or outside portion of the subject's home cage depending on where the subject was likely to spend the most time (e.g., if it was raining or cold, the observation was done inside). For the experimental (i.e., video) condition, the experimenter rolled the computer cart in front of the inside portion of the subject's home cage approximately 3 m from the mesh. The experimenter then sat down, started the videotape, and recorded scratches from a distance of approximately 2.5 m. Most subjects stayed in the area where the experimenter was for the entire duration of the 30 min. However, in order to avoid the possible confounding stress-related effects of being locked inside or separated from their group, no attempt was made to lock animals into a given area during either condition. Thus, animals were free to move into the opposite portion of their cages and to the outdoor portion of their home cage, thus out of view of the experimenter.

The order of presentation of the baseline and experimental conditions was counterbalanced across subjects, with approximately half receiving the baseline condition followed by the experimental condition and the other half receiving the experimental condition

followed by the baseline. A minimum of 12 h separated the presentation of the two conditions to minimize any carryover effects of one condition to the other. Testing was carried out between 4 and 6 o'clock in the evening, typically a very calm and quiet time of day. If testing was done in the morning, then the experimenters made every effort to do both the baseline and experimental conditions at approximately the same time of day.

Scratching was scored in terms of three behavioral parameters: rubs, gentle scratches, and rough scratches (Leavens et al., 2001, 2004). A rub was defined as a self-touch not involving the ends of the digits (RB). A gentle scratch (GS) consisted of a self-touch involving the ends of the digits but no discernable movement of the shoulder joint. Rough scratches (RS) were defined as self-touches that involved the ends of the digits and movement of the shoulder joint. Bouts of scratching were recorded during each condition. The onset of a bout was recorded when the subject used one hand to scratch a part of their body or face. A bout of scratching ended in one of three ways: (1) a self-touching event stopped for a period of 3 s or more, (2) the subject switched hands, or (3) the body region being scratched changed. Inferential statistics were used for all analyses with alpha set to $p < .05$. Post hoc tests, if necessary, were performed with Tukey's HSD.

DNA Extraction, Genotyping, and Analysis

DNA samples were isolated from buccal swabs or blood samples using Puregene DNA purification system (Gentra, Minneapolis, MN) as described by Donaldson et al. (2008). Following extraction, stock DNA was separated into three aliquots: one for onsite storage at −80°C, one for offsite storage, and a working stock for genotyping. Samples were tracked via a secure Filemaker Pro 8 database that linked sample codes for each aliquot, demographics for each subject, DNA quantification and purity analysis results, and genotype data.

Each individual was genotyped for the *AVPR1A* DupA/B region using the primers and conditions reported in previous studies with slight modifications (Donaldson et al., 2008). Briefly, we used forward primer 5'-GCATGGTAGCCTCTCTTTAAT and a reverse primer of 5'-CATACACATGGAAAGCACCTAA with an annealing temperature of 57°C for 30 cycles: 95°C, 5 min; 30 × (95°C, 30 s; 57°C, 30 s; 72°C, 3 min; 72°C, 10 min; 4°C, hold). Polymerase chain reaction (PCR) amplification was undertaken using the Epicentre Failsafe kit using premixH (Illumina Inc., Madison, WI) according to the manufacturer's directions. Genotyping was performed in a volume of 20 μl containing 20 ng target genomic DNA. PCR products were resolved on a 2% agarose gel (SeaKem Agarose LE, Lonza, Basel, Switzerland) at 100 V for 45 min with a 100-bp DNA ladder (New England BioLabs, Ipswich, MA) in tris-borate-EDTA (TBE). The DupB-containing allele resulted in a band of ~900 bp, while the DupB minus allele was ~570 bp long, and genotypes were visually assigned (Donaldson et al., 2008). All genotypes were run in duplicate with gel analysis and were checked before the data set was finalized.

Magnetic Resonance Image Collection and Procedure

Subjects were first immobilized by telazol injection (2–6 mg/kg) and subsequently anesthetized with propofol [10 mg/(kg/h)] following standard procedures at the YNPRC. Subjects were then transported to the MRI facility. The subjects remained anesthetized for the duration of the scans as well as the time needed to transport them between their home cage and the imaging facility (total time ~2 h). Subjects were placed in the scanner chamber in a supine position with their head fitted inside the human-head coil. Scan duration ranged between 40 and 50 min as a function of brain size. The chimpanzees were scanned using a 3.0 T scanner (Siemens Trio, Siemens Medical Solutions USA, Inc., Malvern, PA). T1-weighted images were collected using a three-dimensional gradient echo sequence (pulse repetition = 2,300 ms, echo time = 4.4 ms, number of signals averaged = 3, matrix size = 320 × 320). After completing MRI procedures, the subjects were returned to the YNPRC and temporarily housed alone in a cage for 6–12 h to allow the effects of the anesthesia to wear off, after which they were returned to their home cage. The archived MRI data were transferred to a PC running Analyze 7.0 (Mayo Clinic, Mayo Foundation, Rochester, MN) software for postimage processing.

Voxel-Based Morphometry

For the VBM analysis, we used the three modules developed in FSL (Analysis Group, FMRIB, Oxford, UK; Smith et al., 2004). In our analysis, MRI scans and genotype data were available in 60 chimpanzees including 36 $DupB^{-/-}$ and 24 $DupB^{+/-}$ chimpanzees. Following previously employed VBM methods (Hopkins et al., 2008; Hopkins, Taglialatela, Nir, Schenker, & Sherwood, 2010), images of the individual brains were first skull-stripped and linearly registered to a chimpanzee template brain. Subsequently, each T1-weighted volume was segmented into GM and white matter (WM) volume as well as cerebrospinal fluid. The partial GM volumes were saved and averaged together to create an initial GM template. This initial GM template brain was then flipped on the left-right axis, merged with the native space, and this merged volume was then averaged. Next, each linear transformed volume was nonlinearly registered to the study-specific GM template. The individual nonlinear registered brains were then merged as a single 4D volume, averaged, then the 4D volume was flipped on the left-right axis and saved as a separate volume. The normal and flipped 4D volumes were then averaged to create the final GM template brain. Lastly, each individual nonlinear registered brain was reregistered using a nonlinear registration (FNIRT), and the volume and associated Jacobian warping field were saved as output. The individual nonlinear registered volumes were multiplied by the Jacobian warping field and each saved as a volume. These volumes were then merged into a single 4D volume and smoothed with a 2-mm sigma Gaussian kernel. Voxelwise independent samples t tests ($DupB^{-/-} > Dup^{+/-}$) were performed using the generalized linear model (GLM) function in FSL; age and total brain volume (GM + WM) were included as nuisance covariates. Consistent with previous studies (e.g., Hopkins et al., 2008, 2010), voxel clusters greater than 72 mm^3 with a $p < .01$ were considered significantly different between the $DupB^{-/-}$ and $DupB^{+/-}$ apes.

Voxel-of-Interest Analysis

To examine the association between scratching rates and GM volumes, we used a VOI approach. For each cluster found to be significant in the VBM analysis, we created an object map or mask using the ROI tool in ANALYZE 11.0. The merged 4D volume with the nonlinearly registered, smoothed volumes was then unappended (i.e., unmerged), thereby displaying each individual GM value multiplied by the nonlinear component of the determinant of the Jacobian previously used in the VBM analysis. The individual object maps were then applied to the modulated GM volumes (i.e., the GM probability adjusted for the Jacobian warping field) to determine the average GM intensity for each cluster. Thus, in this analysis, the measure of interest was the mean GM intensity value

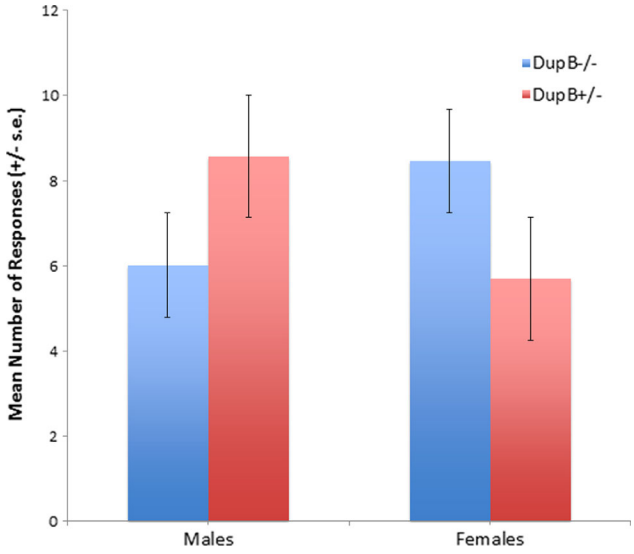

Figure 1. Mean scratching rates (± *SE)* for males and females with the DupB$^{+/-}$ and DupB$^{-/-}$ genotypes.

within each object map. Higher values reflected increased probability that the voxels within the object map were GM. The mean GM intensity values for each object map were computed for each individual chimpanzee, and these values were then correlated with scratching behavior.

Results

Association Between *AVPR1A* and Displacement Behaviors

To test for *AVPR1A* and sex effects on scratching, we performed a mixed model analysis of variance (ANOVA). Condition (video, baseline) and scratch type (RS, GS, and RB) were the repeated measures while sex (male, female) and *AVPR1A* genotype (DupB$^{-/-}$, DupB$^{+/-}$) were the between-group factors. Significant two-way interactions were found between condition and scratch type, $F(2,144) = 6.371$, $p < .003$, and between sex and *AVPR1A* genotype, $F(1,72) = 6.159$, $p < .02$. The mean number of RS, GS, and RB responses in the video and baseline conditions are shown in Table 1. For the Condition × Scratch Type interaction, post hoc analysis with Tukey's HSD correction indicated that the number of RS, GS, and RB responses were significantly higher in the video compared to baseline conditions. Additionally, within the video condition, the number of GS responses was significantly higher than the RS and RB responses. In the baseline condition, GS and RB responses each occurred more frequently than RS responses. To depict the Sex × Genotype interaction, the mean number of scratching responses across the three types of scratching behaviors in male and female DupB$^{-/-}$ and DupB$^{+/-}$ individuals is shown in Figure 1. Post hoc analysis indicated that, for males, DupB$^{+/-}$ individuals showed significantly higher rates of scratching than DupB$^{-/-}$ apes. In contrast, for females, DupB$^{+/-}$ individuals scratched significantly less than DupB$^{-/-}$ apes.

Table 1. *Mean Number of Rough Scratches, Gentle Scratches, and Rubs in the Video and Baseline Conditions*

	Video	Baseline
Rough scratch (RS)	5.125 (0.861)	1.943 (0.353)
Gentle scratch (GS)	14.937 (1.624)	5.764 (0.982)
Rub (RB)	10.711 (1.432)	4.633 (0.463)
Mean all	10.258 (0.929)	4.113 (0.397)

[a]*Note*. $N = 76$. Values in parentheses represent standard errors.

Voxel-Based Morphometry

VBM analyses revealed significant differences between DupB$^{-/-}$ and DupB$^{+/-}$ apes in 12 distinct brain regions, with the largest clusters within the frontal lobe (see Table 2). As shown in Figure 2, seven clusters were in the right hemisphere, in regions corresponding to the central sulcus, superior precentral sulcus/gyrus, dorsal lateral prefrontal cortex (PFC), temporal pole, anterior insula, and the cingulate sulcus. The five clusters in the right hemisphere were in regions corresponding to the medial temporal PFC, dorsal lateral PFC, parietal-occipital sulcus, precentral inferior sulcus, ascending limb of the cingulate sulcus, and the anterior cingulate sulcus.

Associations Between GM Clusters and Scratching

Using the VOI approach described above, we next correlated the individual GM values with rates of overall scratching and rates for each of the more specific RS, GS, and RB responses. For these analyses, we ran partial correlations between the VBM-derived clusters and frequency of RS, GS, and RB responses in the video condition, controlling statistically for scratching in the baseline condition for each type of scratching. Given previous findings of sex-specific associations with *AVPR1A*, separate correlations for responses of each scratching type with GM intensity values for the twelve VBM-identified brain regions were computed for each sex, and the significance of the difference between correlations in each case was evaluated using one-tailed Fisher's *Z* tests (see Table 3). Significant sex differences in associations were found between GS rates and mean GM intensity value for clusters 1, 2, 5, 7, 8, and 11, which corresponded to the right central sulcus, right superior precentral sulcus/gyrus, left dorsal lateral PFC, left precentral inferior sulcus, left ascending limb of the cingulate sulcus, and the right anterior insula, respectively. Correlations in each of these instances were in opposing directions for males and females. For males, increased scratching rates were associated with lower GM values. In contrast, increased scratching rates were positively associated with GM values in the females.

Discussion

Consistent with the NIMH RDoC initiative (i.e., **Kozak & Cuthbert, 2016**), the current study demonstrates the way in which a chimpanzee (*Pan troglodytes*) model provides a unique framework for investigating psychopathology-relevant constructs within the NVS domain through an interdisciplinary approach integrating elements of psychology, ethology, genetics, and neuroscience. Specifically, we systematically investigated genetic and neuroanatomical correlates of individual variation in scratching, a widely studied, well-validated intermediate behavioral phenotype with clear links to the response to potential harm ("anxiety") construct within the NVS domain. Displacement behaviors represent a promising dependent variable for multilevel, systemic neurobiological investigations. Indeed, in both human (Troisi, 1999) and nonhuman primates (Aureli & Whiten, 2003), self-directed displacement activities such as scratching have been consistently observed in the context of negative emotional states including stress, anxiety, and frustration. Scratching is therefore a simple yet promising transdiagnostic phenotype for RDoC-consistent investigations.

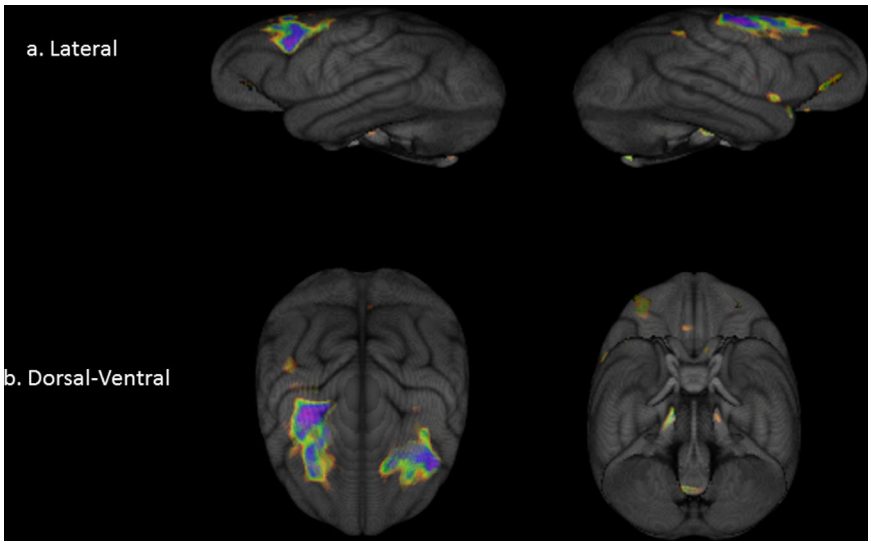

Figure 2. 3D reconstructions of a chimpanzee brain with the significant clusters distinguishing DupB$^{+/-}$ and DupB$^{-/-}$ projected onto the (a) lateral and (b) medial views of the brain surface.

Thus, the current study constitutes a neurogenomics investigation of potential harm response as indexed by scratching behavior across multiple units of analysis. After first demonstrating sexually dimorphic associations between *AVPR1A* and scratching, we next used a VBM approach to identify GM voxel clusters that differentiated *AVPR1A* genotypes. Finally, we examined sex-specific associations between these regions differentiating *AVPR1A* genotypes and scratching. Collectively, the results suggest that sexually dimorphic associations between *AVPR1A* and scratching may be explained by genotype-specific neuroanatomic variation.

In line with both hypotheses and findings using rodent models (i.e., Bielsky et al., 2004, 2005), results suggested sexually dimorphic variation in *AVPR1A* linked to individual variability in scratching behaviors. Specifically, whereas DupB$^{+/-}$ males exhibited significantly more scratching behaviors, for females it was the DupB$^{-/-}$ apes that showed this behavior more frequently. These results are further consistent with previous findings of sexually dimorphic associations between other types of social behaviors (i.e., receptive/joint attention, dominance, pair bonding) and *AVPR1A* polymorphisms in apes (Donaldson & Young, 2008; Hopkins et al., 2014; Latzman et al., 2014) as well as findings suggesting a higher expression of arginine vasopressin in males (Goodson & Bass, 2001).

Table 2. *Significant Gray Matter Cluster Differences Between DupB$^{-/-}$ and DupB$^{+/-}$ Individuals*

	Cluster size	*t*
Cluster 1		
Right central sulcus	759.50	2.97
Cluster 2		
Right superior precentral sulcus/gyrus	2,722.44	2.98
Cluster 3		
Right dorsal lateral PFC	1,228.43	3.31
Cluster 4		
Left medial lateral PFC	261.66	3.07
Cluster 5		
Left dorsal lateral PFC	2,364.74	3.01
Cluster 6		
Left parietal-occipital sulcus	799.9	2.98
Cluster 7		
Left precentral inferior sulcus	73.99	2.66
Cluster 8		
Left ascending limb of the cingulate sulcus	143.08	2.93
Cluster 9		
Left anterior cingulate sulcus	153.86	2.84
Cluster 10		
Right temporal pole	154.84	3.01
Cluster 11		
Right anterior insula	280.77	2.99
Cluster 12		
Right cingulate sulcus	196.00	2.95

Note. $N = 60$. Cluster sizes are in mm^3. The *t* value reflects the average for all voxels within the cluster. PFC = prefrontal cortex.

We also investigated the potential neuroanatomical basis for these *AVPR1A* sex-specific findings. As noted above, there was relatively little data on *AVPR1A* and either neurofunctional or neuroanatomical organization of the brain to guide our analyses (Meyer-Lindenberg et al., 2009; Zink & Meyer-Lindenberg, 2012; Zink et al., 2010). Thus, we utilized a VBM approach to determine the brain regions that differentiate between DupB$^{-/-}$ and DupB$^{-/+}$ individuals. Twelve voxel clusters emerged as significantly different with the largest of these clusters located in the frontal cortex. Findings of differences emerging in the frontal cortex may be consistent with findings of *AVPR1A* expression in regions associated with dopaminergic function and reward pathways (Skuse & Gallagher, 2009). Taken together, in addition to scratching behaviors, results of our VBM analyses suggest that the presence or absence of the RS3-containing DupB element in the *AVPR1A* 5' flanking region is associated with neuroanatomical variation in GM distribution in the frontal lobe. These findings suggest that the differences that emerged with regard to associations between *AVPR1A* variation and scratching behavior may be attributable in part to gene expression caused by the presence or absence of the DupB region in the brain.

To determine whether GM variation in these regions would, in turn, correlate with scratching behaviors, we used a VOI approach to identify GM clusters that distinguished DupB$^{+/-}$ and DupB$^{-/-}$ chimpanzees, and these regions were converted to object maps or masks. We applied these masks to the individually modulated GM volumes, and the intensity of GM within each cluster was quantified and subsequently correlated with individual variation in scratching behavior. Given initial findings of sex-specific associations with *AVPR1A*, correlations were computed separately for each sex and compared. Significant sex differences, with correlations in opposing

Table 3. *Partial Correlations Controlling for Baseline Scratching Between Individual VBM Clusters and Experimental Scratching Rates*

	Males	Females	*Z*	*p*
Cluster 1				
Right central sulcus				
Rough scratch (RS)	+.03	+.31[b]	−1.04	.15
Gentle scratch (GS)	−.35[b]	+.21	**−2.07**	**.02**
Rub (RB)	−.07	+.11	−.65	.26
Mean all	−.26	+.27	**−1.95**	**.03**
Cluster 2				
Right superior precentral sulcus/gyrus				
Rough scratch (RS)	−.12	+.16	−1.01	.16
Gentle scratch (GS)	−.43[a]	+.21	**−2.41**	**.01**
Rub (RB)	+.15	.01	.51	.31
Mean all	−.17	+.17	−1.23	.11
Cluster 3				
Right dorsal lateral PFC				
Rough scratch (RS)	+.05	+.06	−.04	.48
Gentle scratch (GS)	−.13	−.04	−.32	.37
Rub (RB)	+.13	−.09	.79	.21
Mean all	+.01	−.04	.18	.43
Cluster 4				
Left medial lateral PFC				
Rough scratch (RS)	+.09	+.06	.11	.46
Gentle scratch (GS)	−.26	+.04	−1.10	.14
Rub (RB)	.01	−.16	.61	.27
Mean all	−.13	−.07	−.22	.41
Cluster 5				
Left dorsal lateral PFC				
Rough scratch (RS)	+.31	+.25	.23	.41
Gentle scratch (GS)	−.33	+.17	**−1.84**	**.03**
Rub (RB)	+.12	−.13	.90	.18
Mean all	−.02	.11	−.47	.32
Cluster 6				
Left parietal-occipital sulcus				
Rough scratch (RS)	+.17	+.28	−.42	.34
Gentle scratch (GS)	−.09	−.05	−.14	.44
Rub (RB)	+.10	+.29[b]	−.71	.24
Mean all	+.06	+.18	−.44	.33
Cluster 7				
Left precentral inferior sulcus				
Rough scratch (RS)	+.08	+.34[a]	−.98	.16
Gentle scratch (GS)	−.49[a]	+.09	**−2.24**	**.01**
Rub (RB)	.09	−.12	.76	.22
Mean all	−.22	+.09	−1.12	.13
Cluster 8				
Left ascending limb of the cingulate sulcus				
Rough scratch (RS)	−.02	+.32[b]	−1.26	.10
Gentle scratch (GS)	−.41[b]	+.14	**−2.07**	**.02**
Rub (RB)	+.22	−.04	.94	.17
Mean all	−.14	+.15	−1.05	.15
Cluster 9				
Left anterior cingulate sulcus				
Rough scratch (RS)	+.30	−.13	1.58	.06
Gentle scratch (GS)	−.36[b]	−.19	−.66	.25
Rub (RB)	−.01	−.02	.04	.48
Mean all	−.16	−.15	−.04	.48
Cluster 10				
Right temporal pole				
Rough scratch (RS)	−.24	+.04	−1.02	.15
Gentle scratch (GS)	−.42[a]	−.05	−1.42	.08
Rub (RB)	+.00	−.11	.40	.35
Mean all	−.16	−.15	−.04	.48
Cluster 11				
Right anterior insula				
Rough scratch (RS)	−.05	+.20	−.91	.18
Gentle scratch (GS)	−.41[b]	+.16	**−2.14**	**.02**
Rub (RB)	+.05	+.06	−.04	.48
Mean all	−.26	+.18	−1.61	**.05**
Cluster 12				
Right cingulate sulcus				
Rough scratch (RS)	+.18	+.18	.00	.50
Gentle scratch (GS)	−.25	+.14	−1.42	.08
Rub (RB)	+.04	+.01	.11	.46
Mean all	−.13	+.12	−.90	.18

Note. PFC = prefrontal cortex; *Z* = Fisher *Z* statistic. Values under *p* heading reflect one-tailed probability (significance) level for the *Z* statistic with $p \leq .05$ shown in boldface.
[a]value of *r* for which *p* was significant at $< .05$.
[b]value of *r* for which *p* was significant at $< .10$.

directions for males and females, were found between GS scratching rates with the mean GM value for the clusters within six of the 12 VBM-identified regions. Specifically, whereas increased scratching rates were associated with decreased GM values for males, increased scratching rates were associated with increased GM values for females. Findings of associations with the frontal cortex as well as the insula may not be entirely unexpected. Indeed, given its links to sympathetic nervous system activity, recent research suggests that this region is particularly important in the appraisal of negative emotions (for a review, see Etkin, Egner, & Kalisch, 2012).

In summary, results of a systematic investigation of multiple units of analysis (i.e., genes, physiology) suggest a sexually dimorphic neurogenomic basis for scratching behaviors in chimpanzees. Our findings indicate that a genetic polymorphism found to be associated with a RDoC-relevant phenotype is differentially associated with GM variation, which, in turn, correlates with the phenotype. Specifically, after finding sex-specific associations between scratching behaviors and polymorphisms in the *AVPR1A* gene, we identified regions of the brain that differentiated between *AVPR1A* genotypes, which were then found to evidence sex-specific correlations with scratching.

A key but important finding in this report was the observation of sex differences in both (a) the influence of the RS3 polymorphism on scratching behavior, and (b) the association between scratching behavior and GM values that distinguish $DupB^{+/-}$ and $DupB^{-/-}$ chimpanzees. It is important to recognize that variation in the RS3 polymorphism does not differ between males and females; thus, it is the functional consequences of this polymorphism that appear to influence their behavior. Alternatively, it may be the case that the influence of the RS3 polymorphism manifests itself behaviorally in sex differences in responding to stimuli of the distinct types used in this study (i.e., recorded social encounters). It might be the case that seeing and hearing unfamiliar chimpanzees squabble and negotiate over a watermelon evokes a differentially valenced response in male and female chimpanzees, depending on their RS3 genotype. In other words, $DupB^{+/-}$ male and $DupB^{-/-}$ female chimpanzees may interpret the interactions in a negative manner but for different reasons. For $DupB^{+/-}$ males, which we know from previous research appear to be high ranking (Hopkins, Donaldson, & Young, 2012), the reaction to the stimuli may be defensive and one which reflects their motivation to protect other group members. In contrast, we know from previous results (Hopkins et al., 2012), that $DupB^{+/-}$ females tend to be low ranking; their anxiety may be therefore due to a threat of physical harm from an unfamiliar chimpanzee. Unfortunately, we cannot address this issue in this study because, although scratching behavior clearly measures anxiety responses in the chimpanzees, it does not distinguish the underlying motivation for the anxiety.

There are some limitations to this study, and therefore the findings should be interpreted as an initial approach to a complex issue. First, notably, the current study included a relatively modest-sized sample resulting in limited statistical power. As has been described previously (e.g., Hewitt, 2012; Iacono, Malone, Vaidyanathan, & Vrieze, 2014; Ionnidis, Ntzani, Trikalinos, & Contopoulos-Ionnidis, 2001), the replicability of findings, particularly candidate gene findings, in small- to moderate-sized samples is always a concern. The current findings will therefore need to be replicated in independent samples. Second, though VBM has many strengths, it does have some drawbacks, particularly with regard to interpreting how regional differences in GM intensity map onto more concrete neurological traits, such as volumetric differences or cortical thickness. Nonetheless, our VBM results point to cortical regions that should be targeted for ROI analyses or potentially histological studies. Third, the focus in this study was on anatomical differences between $DupB^{+/-}$ and $DupB^{-/-}$ chimpanzees as they relate to scratching behaviors, but these results do not speak to the function of these cortical regions. Fourth, it would be useful to explore the potential influence of more specific types of affective stimuli on scratching behavior in the chimpanzees. Recall that we used video scenes that were highly variable in the types of affective information displayed because there was a mixture or blending of both negative (e.g., screams, mild aggression) and positive (e.g., food calls, pant-grunts) valence signals. Using video scenes that were exclusively positive or negative may have produced more specific responses in the chimpanzees. Finally, the occurrence of scratching behaviors of the apes in the video scenes was not recorded. Thus, the potential of contagion of scratching (i.e., Nakayama, 2004) was not able to be examined.

These limitations notwithstanding, the current study clearly demonstrates a novel way in which the RDoC NVS domain can be meaningfully studied in chimpanzees, an animal model uniquely well suited for multilevel neurobiological investigations of RDoC-relevant domains and constructs. The current work can serve as an example for future innovative research directed at elucidating core neurobiological processes of various RDoC domains and constructs across multiple units of analysis (e.g., genes, circuits, physiology, behavior). Importantly, although the current study focused specifically on one construct within the NVS domain, results from the current study provide clear support for primate-translational operationalizations of the various RDoC domains and constructs represented in the RDoC framework. Whereas there have been recent decisions to scale back some types of research with captive chimpanzees by NIH (NIH, 2011), studies such as the current study fit well within the ethical framework of scientifically justifiable research with chimpanzees outlined by the Institute of Medicine (2011). In sum, along with work simultaneously being conducted on other RDoC-relevant domains (e.g., Latzman et al., 2015), the current research highlights the importance of including a comparative-translational component, as exemplified by multidomain findings from protohuman subjects (i.e., chimpanzees), in the NIH RDoC research program. In conjunction with findings from human studies, work of this kind can provide enormously valuable insights into core biobehavioral processes relevant to psychological illness and health.

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