Preface

I wrote this paper in graduate school, but it remains highly relevant to User Experience, Customer Experience, and Human Factors research today, as it allows for the comparison of categorical and continuous data in the same variance space, thus bridging the gap between "quant" and "qual" data, all for the end goal of better understanding our customers.

A word to the wise (that most other users of such methodologies frequently forget to mention): transposing categorical data into continuous dataspace, by definition, includes a degree of subjectivity. This is allowed only under the assumption that the analyst is binning their data appropriately and in good faith.

The rationale and code for this study could easily be applied in business situations such as:

- *Identifying relationships between user rating data (e.g., Likert scale data treated as categorical data) and reaction time (e.g. milliseconds until clicking on the intended target)*
- *Operations in physical space and number of attempts to complete a task successfully (e.g., a forklift operator must shift their eye gaze X degrees from a primary focal point to a secondary focal point in order to see a target and successfully maneuver their machinery to pick it up. Success in this case would be measured by number of attempts before picking up the object*

Partial Least Squares Correspondence Analysis for Analysis of Genetic Predictors of Negative Affect in Cannabis Users

A proof of concept study combining categorical and continuous data

Ariel Ketcherside, MSc

Introduction

Cannabis is the most frequently abused illicit drug in the United States ((NIDA), 2013) and approximately 9% of individuals who try cannabis will become dependent on it (Budney, Roffman, Stephens, & Walker, 2007).

Anxiety and depression, as disorders of interoception, exteroception, emotion regulation, and mood homeostasis, are highly comorbid (Morilak & Frazer, 2004). Because of their common etiology, symptoms, and molecular signaling pathways, I have chosen to combine them under the term "negative affect" to better account for dysregulation of limbic systems, whether manifested as hyper- or hypo- functioning.

Affective disorders are especially common among drug users, which is likely due to their common neurocircuitry. Approximately 20% of individuals who have an affective disorders are

also drug dependent, and about 30% of drug dependent individuals are also afflicted with an affective disorder (Conway, Compton, Stinson, & Grant, 2006). This is not surprising, as systems involved in emotional regulation and reward processing are implicated in affective disorders, targeted by drugs, and notably disrupted in the case of drug dependence (Akirav & Fattore, 2011; Hovens et al., 2012).

Cannabinoid Signaling and the Limbic Hypothalamic Pituitary Adrenal Axis: The Limbic[1] Hypothalamic Pituitary (LHPA) Axis is a complex neuroendocrine network that controls individuals' emotional and stress responses to stimuli. Although endogenous cannabinoids are ubiquitous and diverse in their signaling roles, substantial evidence supports a specific regulatory role of the HPA axis (Tasker, 2004). Cannabinoids modulate glutamatergic input to the hypothalamic paraventricular nucleus (PVN), thereby regulating secretion of hormones including corticotropin releasing hormone (CRH) (Di, Malcher-Lopes, Halmos, & Tasker, 2003). Studies of LHPA reactivity in individuals with major depression have shown that abnormalities are present even before symptoms of depression appear. This suggests that the issue begins with the HPA axis itself; that there may be inherent abnormalities potentially attributed to genetic variation (Holsboer, 2000). Thus, it is likely that individuals who have greater overall negative affect would try to mitigate their stress by regulating their own HPA axes via exogenous cannabinoids.

Negative Affect and Cannabis Use

The comorbidity between negative affect and cannabis use has been extensively documented in other studies, specifically the role of negative affect in promoting cannabis use, as a means of self-medication (Bonn-Miller, Vujanovic, Boden, & Gross, 2011; Chabrol, 2005; Conway et al., 2006). For example, Bonn-Miller et al (2011) found a mediation effect of emotion regulation on the relationship between post-traumatic stress disorder and coping-oriented cannabis use (Bonn-Miller et al., 2011). Johnson et al. similarly found that coping motives for MJ use mediated the relationship between anxious arousal and frequency of MJ use (Johnson, Bonn-Miller, Leyro, & Zvolensky, 2009). In all, these findings support the inference of cannabis use as a coping mechanism for negative affect.

My previous work has focused specifically on problematic cannabis use in this context, which indicates the presence of a cannabis use disorder (Gerstein & Lewin, 1990). Substantial evidence supports the fact that stress and trauma during developmental stages have long-term implications on emotional processing (C. Heim & Binder, 2012). This study specifically examined two components of stress: early life stress (McFarlane et al., 2005), and perceived stress (Cohen, Kamarck, & Mermelstein, 1983). For simplicity of discussion, this project refers to these together (as the demonstrate the same trends in our sample) as "stress". In this analysis, I identified a mediation effect of negative affect on the relationship between stress and problematic cannabis use (Ketcherside, 2013). However, some individuals may be more prone than others, due to genetic predisposition. This genetic component of negative affect and heavy cannabis use remains to be identified, thereby prompting the analysis discussed here.

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[1] Because the Bed Nucleus of the Stria Terminalis (BNST) is a substantial output pathway of the amygdala and has been shown to regulate the Hypothalamic-Pituitary-Adrenal Axis, thus supporting the integration of a limbic component in this signaling pathway (Choi et al., 2007).

Genetic Factors

Genetic variation leads to variations in molecular mechanisms; the production of proteins that dictate how well cells and systems do their jobs. Single Nucleotide Polymorphisms (SNPs) account for a substantial amount of the variation between individual human genomes. With advances in genotyping technology, it has become easy and cost effective to identify alleles for SNPs in individuals. In this study, eight SNPs were chosen *a priori* based on their prevalence and proposed functional roles in the literature.

Cannabinoid genes: Variations in the cannabinoid receptor 1 (CNR1) gene have been associated with increased predisposition to cannabis dependence (Akirav & Fattore, 2011; Filbey, Schacht, Myers, Chavez, & Hutchison, 2010). Understandably so, because CB1 expressing neurons promote dopaminergic release in the nucleus accumbens, when activated (Filbey et al., 2010; Schacht, Hutchison, & Filbey, 2012). This is particularly relevant in instances of negative affect, as CB1-expressing neurons in limbic regions have been shown to modulate emotional processing, in conjunction with dopamine D1 receptors (Akirav & Fattore, 2011; Terzian, Drago, Wotjak, & Micale, 2011). Variation in the CNR1 SNP rs1049353 has specifically been associated with resistance to depression treatments (Domschke et al., 2008). In a previous study involving this same sample, our group found that variation in this SNP accounted for a substantial amount of variance in hippocampal and amygdalar volumes, in conjunction with a tendency toward cannabis dependence (Schacht et al., 2012). Two other SNPs in CNR1, rs6454674 and rs806368, have similarly been associated with substance use dependence including alcohol, cannabis, and cocaine (Hopfer et al., 2006; Schacht et al., 2012; Zuo, Kranzler, Luo, Covault, & Gelernter, 2007).

Serotonin: Serotonergic circuitry is best known for its role in feelings of well-being. Serotonin levels are often compromised in individuals with negative affect, accounting for the great success of medications targeting synaptic serotonin in the brain (Baldwin & Rudge, 1995). The serotonin transporter is particularly implicated in mood and stress response regulation, and is a hallmark target for treatment of emotional regulation disorders (Ketcherside, 2013). As a result, its encoding gene solute carrier 4 A6 (SLC4A6) has been examined for polymorphisms associated with pathology. The SLC4A6 SNP rs2066713 was specifically chosen for this analysis, because is a fragment length polymorphism in the serotonin transporter gene (Dong, 2009). In addition, rs6311 is included because it is in the promoter region for the Serotonin Receptor 2A (HT2RA) gene. The minor allele at this locus decreases usage of an upstream transcription start site , encoding a longer 5'UTR with greater translation efficiency (Smith RM, 2013). The serotonin receptor 2A (HT2RA) is an excitatory receptor specifically associated with anxiety. Some studies have indicated that rs6311 is implicated in major depressive disorder (MDD), but the results remain inconclusive (Kishi et al., 2010).

LHPA Axis: An inability to cope with stress is an integral component of addiction development (Renoir, Pang, & Lanfumey, 2012). Because of this, I examined risk alleles in the LHPA axis. Adrenergic receptor beta(2) (ADRB2) became especially relevant, as implicated in psychological (and physiological) responses to environmental stress. It is a principal binding site for epinephrine, and is thereby a worthy candidate for examination of HPA axis dysregulation. For this analysis, I examined rs1042713, also known as Arg16Gly. It is a non-synonymous polymorphism, which results in agonist-induced internalization of the ADRB2 receptor (Diatchenko et al., 2006).

Dopamine: Dopaminergic circuitry is known for its role in reward. Specifically dopaminergic neurons in the ventral tegmental area and nucleus accumbens have been identified as recognizing and pursuing rewarding stimuli. These same neurons are also associated with avoiding negative stimuli (Budney et al., 2007; Koob & Le Moal, 2008) and may therefore play a role in a genetic predisposition toward negative affect that would be mitigated by cannabis use.

Catechol-*O*-methl transferase (COMT) is the most well-known enzyme that degrades dopamine, epinephrine, and norepinephrine (Alexander et al., 2011; Mier, Kirsch, & Meyer-Lindenberg, 2010). As a result, variations in its sequence are also potentially relevant to mood dysregulation and drug use problems. Two COMT SNPs, rs165722 and rs4646312, have been associated with increased novelty seeking behavior (Roe et al., 2009) and are therefore included in this analysis. Excessive novelty seeking behavior is a risk factor for drug use, especially if comorbid with negative affect (Kreek, Nielsen, Butelman, & LaForge, 2005).

There are approximately 10 million SNPs in the human genome. Greater understanding of differences in genetic makeup could elucidate greater understanding of how we function in our daily lives. The latter is quantified through self-report measures in this study, and I aspire to identify how they are related. If we can identify genetic correlates for behavior like negative affect and cannabis use, we will be better equipped to treat both. For example, a medication that targets specific receptors or blocks transporters could be most effective in individuals with neurochemical imbalances in these specific pathways We would also have preemptive knowledge regarding potential for drug use disorder development, which might alter decisions people made about life choices like drug use initiation.

For Analysis: Each individual has two sets of chromosomes; one from each parent. This means they have three possibilities for their genotype in a specific SNP, specifically in terms of the allele that has been associated with drug use disorders or negative affect according to previous literature (i.e. the “risk” allele). They can be homozygous for this allele, heterozygous (one copy of the gene has the risk allele and the other doesn’t) or homozygous for a major/non-risk allele. Although the number of risk alleles can be counted, the allele is still a categorical variable in nature: function of the allele is not linearly related to genotype. For example, genotype for the Val158Met polymorphism in the COMT gene has demonstrated numerous times an inverted U pattern in function (Cools & D'Esposito, 2011; Tan, Callicott, & Weinberger, 2007). This importantly dictates the manner in which we must examine SNPs from a statistical perspective: as categorical rather than quantitative variables, since the presence of 0, 1, or 2 minor alleles does not indicate a linear change in function.

Table 1: SNPs of interest in this analysis.

SNP	Gene	Function	Minor Allele	% Minor Allele in Sample (Aa or aa)	% Homozygous Minor Allele in Sample (aa)
rs1049353	CNR1	Resistance to depression treatment	A	46	2
rs6454674	CNR1	Substance use disorders	G	57	14
rs806368	CNR1	Substance use disorders	C	39	9
rs1042713	ADRB2	Receptor internalization	A	60	13

rs2066713	SLC4A6	Fragment length polymorphism	T	65	14
rs165722	COMT	Novelty seeking behavior	T	67	22
rs4646312	COMT	Novelty seeking behavior	C	60	14
rs6311	SLC4A6	Reduced transcription efficiency	T	58	14

Behavior measures are likewise coded nominally because the presence or absence of one person's anxiety is different from the presence or absence of another person's.

Partial Least Squares Correspondence Analysis

Partial Least Squares Correspondence Analysis (PLSCA) is a new statistical method especially suited for identifying commonalities between genetics and behavior. It is a combination of two methods and draws upon specific aspects of each of them:

Partial Least Squares Analysis (PLS) allows for the analysis of two tables of data that describe the same observations. In this case, each participant is an "observation", with genetics as one table to be analyzed, and behavior data (depression and anxiety) as another. This poses a problem, however, because both of these tables of data are nominal, and PLS is suited for quantitative data.

The second part of PLSCA, Correspondence Analysis (CA), is a form of Partial Least Squares specifically for nominal data. CA allows for analysis of one table of data, typically with rows denoting observations, and columns denoting variables for which each observation has a value (D. Beaton, Filbey, F., Abdi, H., 2013a).

PLSCA allows for the analysis of two tables of nominally-coded variables, each set in its own table, that describe the same sample by combining the merits of Partial Least Squares Analysis (PLS) and Correspondence Analysis (CA). The two tables of data to be analyzed are denoted as matrices X and Y. Table X consists of I by J rows, and table Y consists of I by K rows, where I represents the observations they have in common. When multiplied together (X^TY), this makes the matrix R, of dimensions JxK:

$$ {}_JR_K = {}_IX_J^T{}_IY_K $$

Because these data is nominal, analysis must occur in an accommodating framework. Thus, X^2 is used, allowing data to be characterized according to its marginal probabilities (D. Beaton, Dunlop, J., Abdi, H., Alzheimer's Disease Neuroimaging Initiative, 2013).

The goal of PLSCA is to identify commonalities in variance between two tables of nominal data. To do this, the original data tables (X and Y) are multiplied by the left and right singular vectors, U and V (respectively), which are themselves obtained from the singular value decomposition of X and Y. The products of XU and YV are latent variables (L_X and L_Y). These latent variables are orthogonal, and the manner in which they are scaled allows them to be plotted together, on the same graph (called a bipolot), thereby allowing for visualization of their relationship (D. Beaton, Filbey, F., Abdi, H., 2013b).

By examining these variations in conjunction with indicators of negative affect, I aim to identify if heavy cannabis users with negative affect are more likely to have risk alleles for the above mentioned genes, thereby indicating that there is genetic predisposition for their condition (Naqvi & Bechara, 2010). PLSCA will allow these tables of data to be analyzed in the same space, so differences and similarities in variables can be visualized.

Methods

Participants: Participants from this study took place in a larger study investigating neural mechanisms related to cannabis abuse and dependence (details in (Filbey, Schacht, Myers, Chavez, & Hutchison, 2009). As part of the study, cannabis users (CU) completed questionnaires pertaining to demographics, cannabis use, negative affect, and stress. They also performed neuropsychological assessments, underwent an MRI scan, and provided a saliva sample for genotyping. Healthy controls (HC) completed the same measures, except those regarding cannabis use. All participants were recruited from the Albuquerque, New Mexico metro area via media advertisements to participate in studies that focused on determining the neurobiological antecedents of substance use disorders. Overall, 157 CU and 37 HC were recruited. The Institutional Review Board of the Mind Research Network approved all of the recruitment and experimental procedures.

Inclusion/Exclusion Criteria: All participants were required to give written, informed consent to participate in the study. They were also required to be right handed, between the ages of 18 and 55, with no MRI contraindications (e.g. pregnancy, metallic implants in the body, claustrophobia, etc.). All participants were required to use no substances besides cannabis (CU only), nicotine, and alcohol, as verified via phone screen before the appointment. At the appointment, this was further verified by urine toxicology analysis, and thorough interrogation regarding all drug use for the past 90 days. Only CU positive for THC and HC negative for THC were included in this study. All participants were required to have no history of psychosis according to the Psychotic Symptoms module of the Structured Clinical Interview for DSM-IV-TR, Research Version (SCID-TR) (First, 2002).

Outcome measures: To determine the relationship between negative affect, emotion regulation, stress, and cannabis/alcohol use, I analyzed responses to the Beck Anxiety Inventory (BAI) (Creamer, Foran, & Bell, 1995), Beck Depression Inventory (BDI)(Steer, Beck, Riskind, & Brown, 1986).

Experimental Design/Analysis: Data was preliminarily analyzed for the distribution of each variable, as this would affect measure outcomes. All variables were binned to make nominal for this analysis, and to eliminate the contribution to the variance caused by outliers.

Multiple Correspondence Analysis (MCA) was used to associate quantity and severity of negative affect (BAI, BDI). First, responses to each of the 21 questions in each inventory were re-coded to simply the presence of or absence of a positive report for that symptom. The data underwent MCA to identify patterns of relationships between measures of depression and anxiety. The scarce responses to some symptoms (ex: feelings of choking) resulted in an exaggerated first component, so I performed the MCA with a Hellinger distance rather than chi-square distance correction to account for this (Figure 1) (Abdi, 2007).

Negative Affect is represented as scores on the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BDI). Problems associated with cannabis use are represented

according to the Marijuana Problem Scale (MPS). Questions were answered by 0-3, with 0 indicating “this symptom does not affect my life” to 3 indicating “this symptom affects my life so much I could not stand it”. To eliminate the effect of imbalanced presence of responses, these were recoded to simply reflect the presence or absence of negative affect; either as a “yes” or a “no”.

Partial Least Squares Correspondence Analysis was used to identify relationships between negative affect and SNPs associated with substance dependence and emotional dysregulation in the literature. Inference tests (a permutation test and a bootstrap ratio test) were performed to identify how likely these results were to occur by chance.

Results

MCA: There were 49 components, three of which were significant. Component 1 explained 26.33% of the variance, with an associated eigenvalue of 1.13E-3, p=0.01. Component 1 clearly differentiates the presence of negative affect (on the right side of the graph) from the absence of negative affect, on the left. Component 2 explained 7.45% of the variance, with an associated eigenvalue of 3.20E-4, p=0.01. This component differentiates the presence of anxiety from the presence of depression. These results support the use of these inventories as adequate indicators of depression and anxiety, so I proceeded to analyze these measures in conjunction with SNPs of interest (Figure 1).

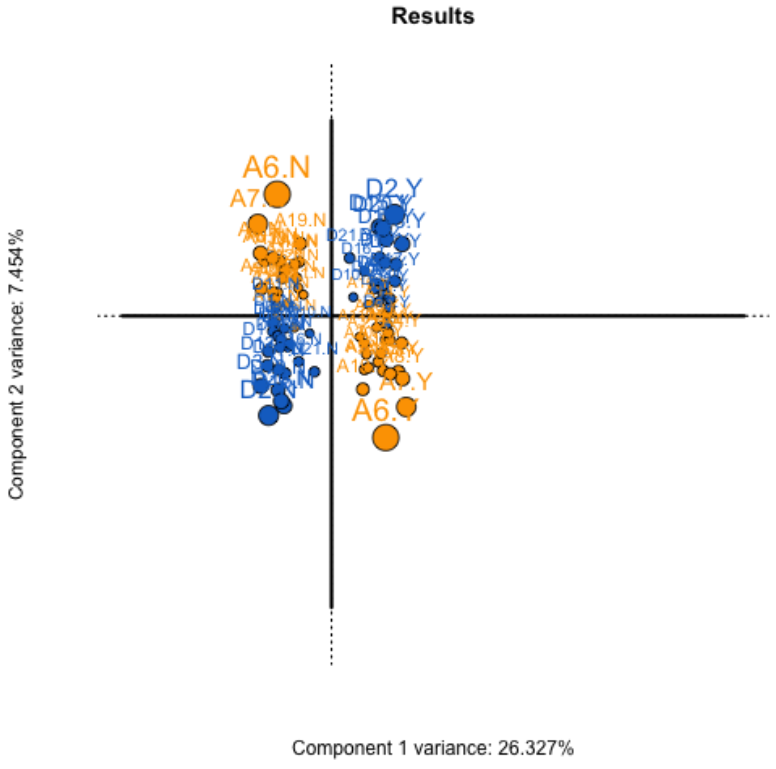

Figure 1: Multiple Correspondence Analysis of negative affect, components 1 and 2.

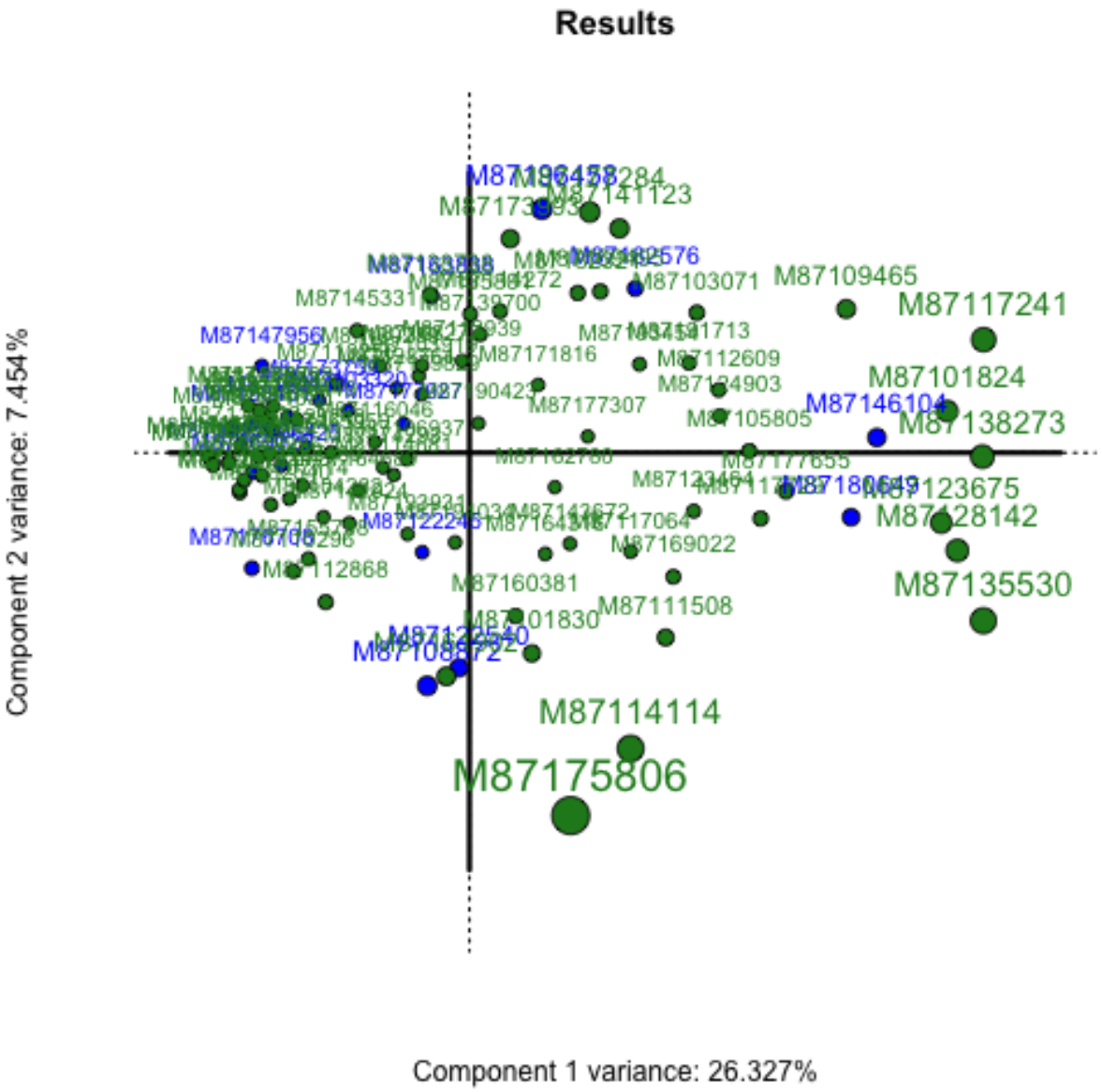

Figure 2: MCA of Participants along components 1 and 2. Distribution of MUs (green) and HCs (blue) shows a relatively homogenous distribution along components 1 and 2,with proportionally more MUs (43%) than HCs (22%) on the side associated with the presence of negative affect. Although there are proportionally more MUs (46%) than HCs (39%) on the bottom of component 2 than on the top, the distribution of each group is more equal than along component 1.

Component 3 explained 5.89% of the variance, with an associated eigenvalue of 2.53E-4, p=0.01. This component differentiates somatic (ex: “indigestion”, feeling hot”, etc.) from

psychological afflictions (ex: “self dislike”, “self criticalness”, “fear of worst happening”, etc.). (Figure 3).

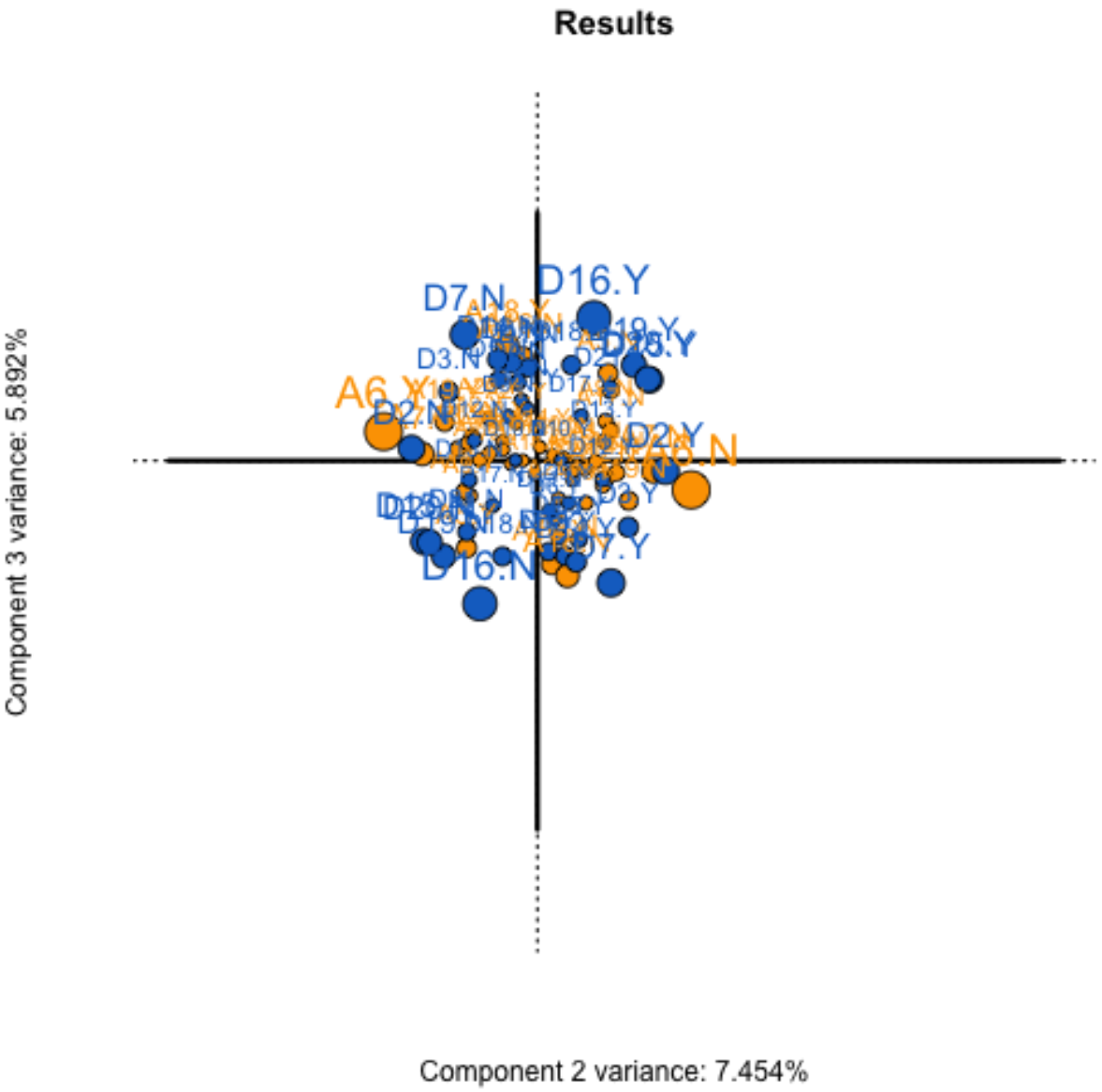

Figure 3: MCA of Negative Affect along components 2 and 3.

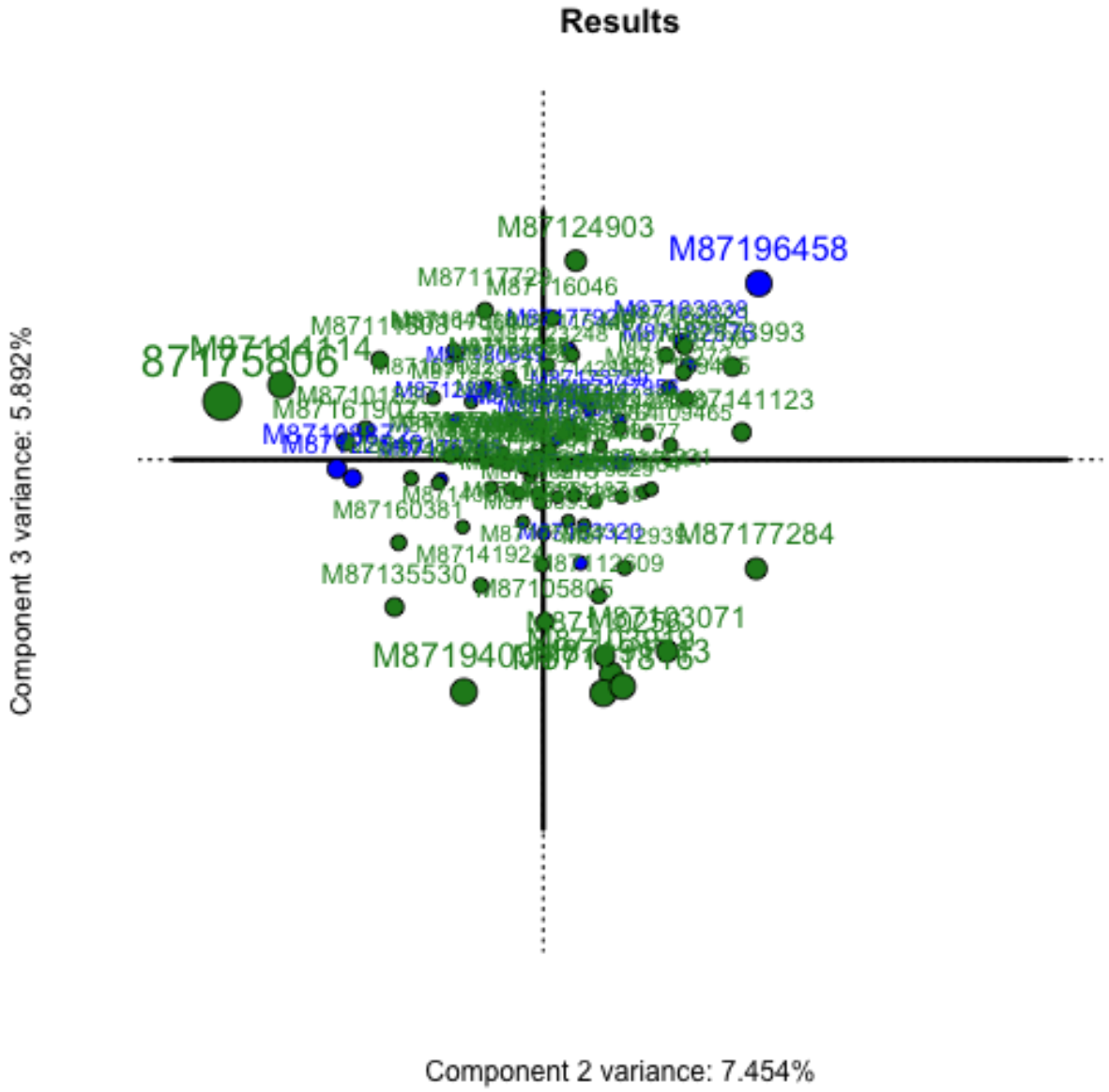

Figure 4: MCA of Participants along components 2 and 3.

PLSCA: After an initial MCA demonstrated the relationship between the absence and presence of depression and anxiety, a PLSCA was performed to show how these fit with participants' genotypes. There were 16 different components, none of which were significant ($p_{omnibus}$=0.529). Component 1 explained 25.31% of the variance, with an associated eigenvalue of 4.82E-3, p=0.718. Component 2 explained 16.24% of the variance, with an associated eigenvalue of 3.10E-3, p=0.198.

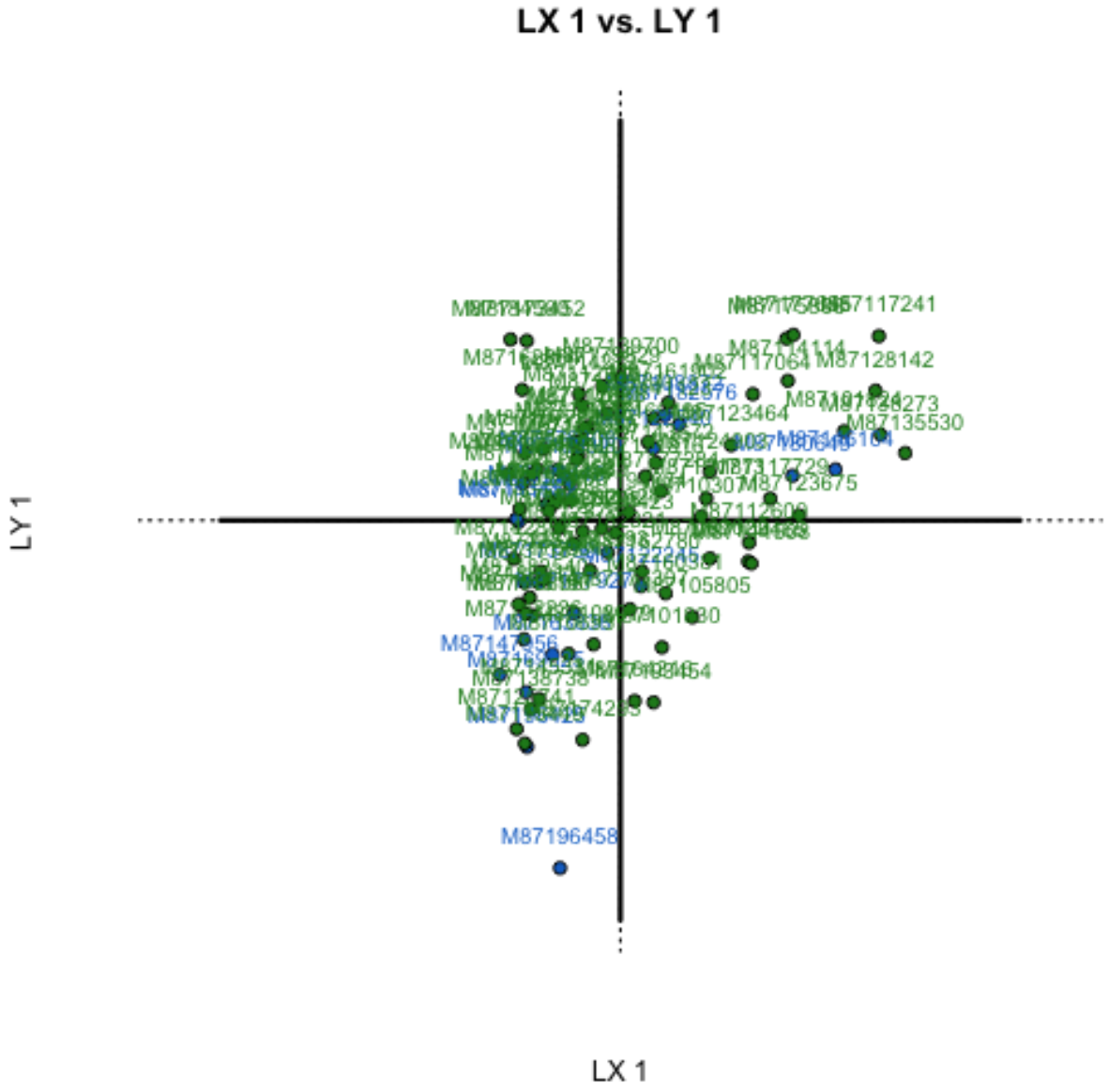

Figure 5: Latent Variables of Table X (Depression and Anxiety) plotted against latent variables of Table Y (SNP alleles).

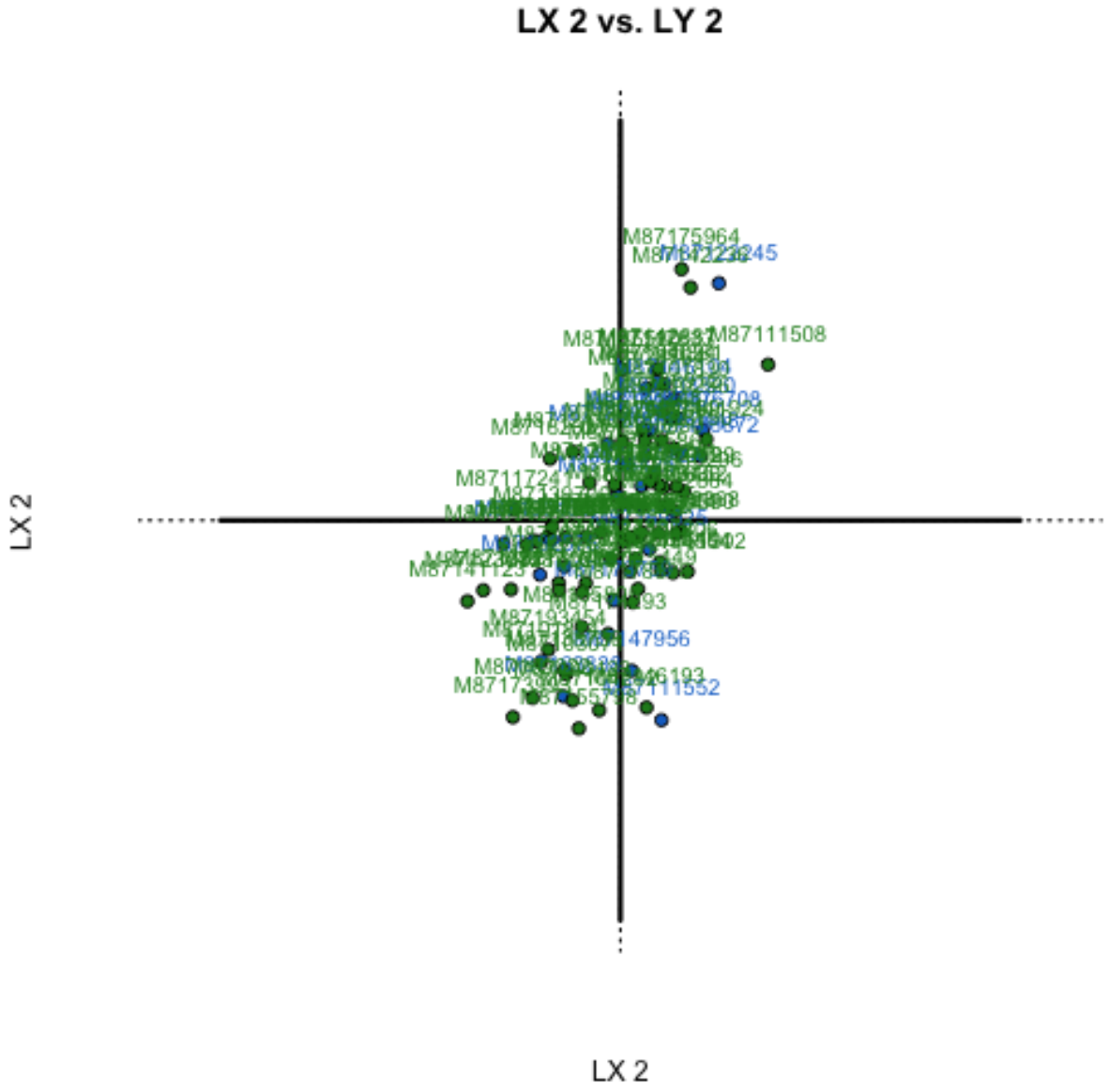

Figure 6: Latent variables of Table X (Depression and Anxiety) plotted against latent variables of Table Y (SNP alleles). The greatest amount of variability occurs along the Y axis.

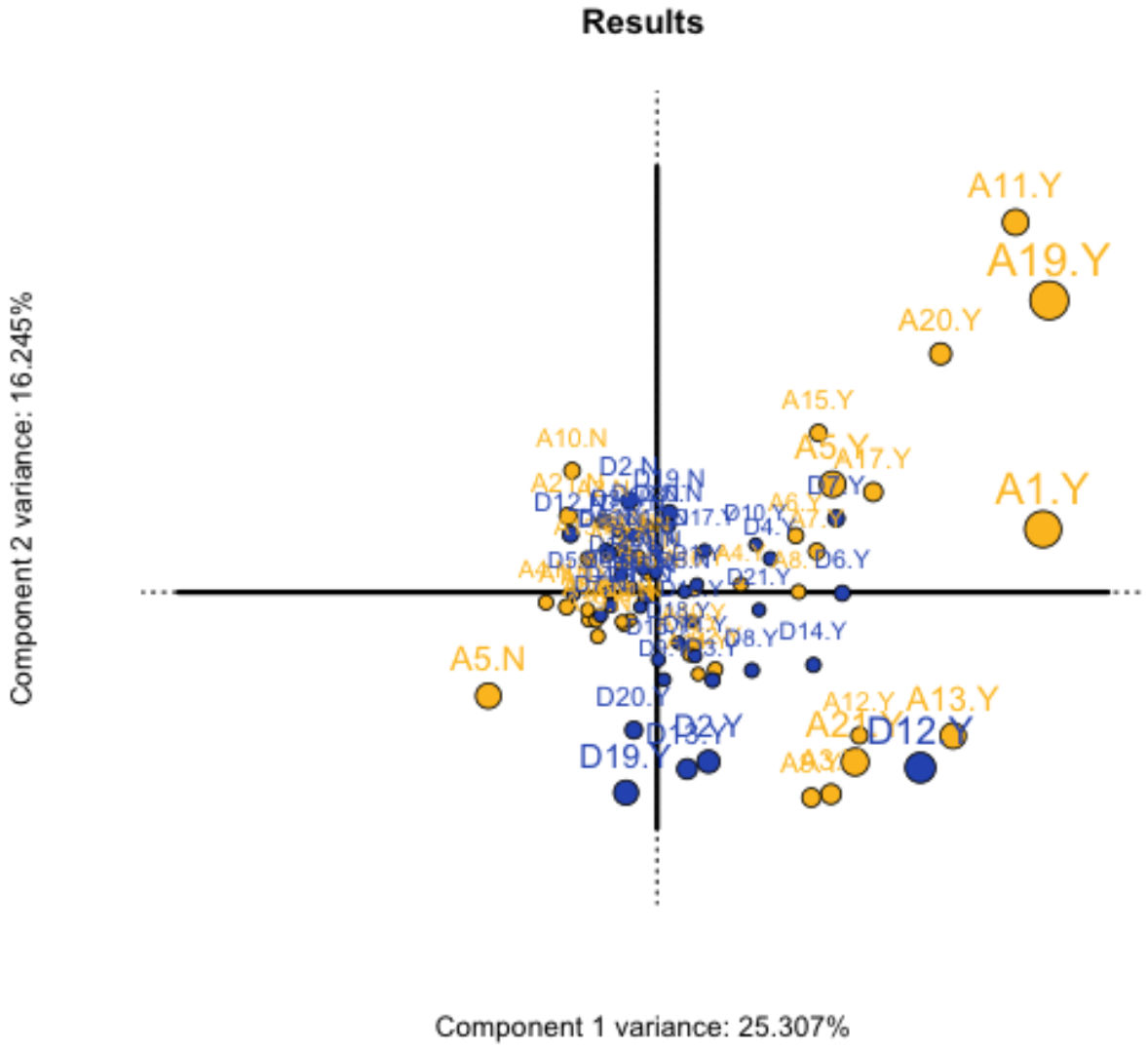

Figure 7: PLSCA analysis of negative affect along components 1 and 2 demonstrates that the presence of anxiety symptoms 1, 11, 19, and 20 account for the greatest difference, as depicted in its distance from the barycenter.

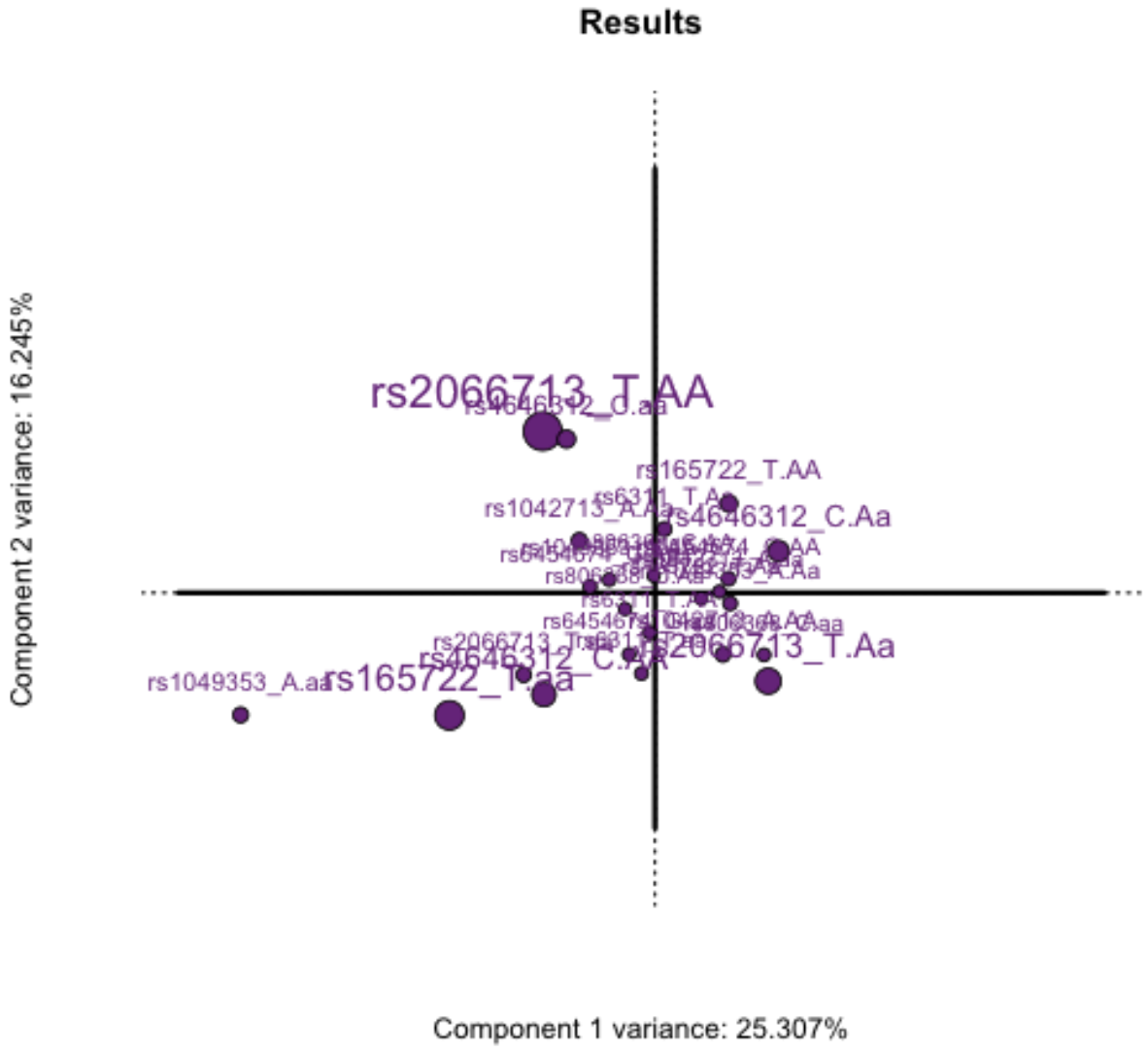

Figure 8: SNP status as homozygous for risk allele, heterozygous, or homozygous for dominant allele.

Because these results were inconclusive, a post-hoc Chi square test for distribution of means was performed, with a p value simulated by Monte Carlo procedures (X^2=639.88, p=1). Bootstrap confidence intervals were calculated to determine bootstrap ratios that would identify which relationships between scores and variables were unlikely to happen by chance.

Permutation tests were used to identify the likelihood of obtaining these results by chance. Because none of the results were less likely than 1/1000 permutations to happen, all components are considered insignificant.

Discussion

In this study, I examined eight SNPs that are identified in the literature as being associated with symptoms of negative affect and/or drug use disorders. This study indicates that variations in these SNPs is not implicated in negative affect presented in this sample of heavy cannabis users.

The heavy cannabis users in this study who have genetic predispositions to negative affect may have been ruled out during data preprocessing, because they demonstrated no symptoms of negative affect. This would support the self-medication hypothesis of drug use, and these individuals could be considered to be successfully self-medicating, since they demonstrate no acute symptoms of depression or anxiety.

Negative Affect and Stress. Early life stress and perceived stress have been shown to prompt hyperactivity in the amygdala (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011), downregulation of serotonergic modulation of the HPA axis (C. Heim & Binder, 2012) and cognitively, excessive rumination (Nolen-Hoeksema, 2000). These result in negative affect, which prompts cannabis use as a means to self-medicate.

However, other studies have found increases in peripheral corticotrophin-releasing hormone (CRH) and glucocorticoid resistance in victims of early life stress (C. Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; C. Heim, Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008). This indicates the up-regulation of the limbic hypothalamic pituitary adrenal (LHPA) axis, in an effort to cope with increased environmental stress.

Faulty *a priori* hypotheses regarding the function of rs2066713 may be responsible for its lack of a significant result. Further research on the definition of a “fragment length polymorphism” demonstrated that it is not in fact a polymorphism that results in a shorter protein, but rather a polymorphism that creates an identifiable fragment when cleaved with restriction enzymes. Thus, this polymorphism is not in fact related to any of these psychopathologies in the literature beyond its function in laboratory identification procedures.

Conclusions

Further research is necessary. A larger sample size is required to accurately capture the genetic variation present in the population, before conclusions can be made about the distribution of minor alleles in conjunction with negative affect. More SNPs should also be examined, as none of these mechanisms are likely to depend on one locus of genetic variation.

A more precise measure of negative affect is also necessary; one that asks about lifetime symptoms rather than the symptoms in the past two weeks. In addiction, symptoms should be considered only when the individual is not under the influence of or withdrawing from cannabis – which would be difficult in a population of heavy users who are possibly dependent.

Future analyses will incorporate more dimensions that may capture symptoms of negative affect, for example, the NEO Five Factor Inventory, the State Trait Anxiety Inventory, the Marijuana Motives Measure, and other measures of factors that could indicate how negative affect and drug use are related. In summary, more information is needed to make any conclusions.

Appendix 1: Negative Affect Measure Key

Table 1: Variable key for items from the Beck Depression Inventory and Beck Anxiety Inventory

Beck Anxiety Inventory		Beck Depression Inventory	
bai1	numbness or tingling	bdi1	sadness
bai2	feeling hot	bdi2	pessimism
bai3	wobbliness in legs	bdi3	past failure
bai4	unable to relax	bdi4	loss of pleasure
bai5	fear of worst happening	bdi5	guilty feelings
bai6	dizzy or lightheaded	bdi6	punishment of feelings
bai7	heart pounding/racing	bdi7	self dislike
bai8	unsteady	bdi8	self-criticalness
bai9	terrified or afraid	bdi9	suicidal thoughts/wishes
bai10	nervous	bdi10	crying
bai11	feeling of choking	bdi11	restlessness
bai12	hand trembling	bdi12	loss of interest
bai13	shaky/unsteady	bdi13	indecisiveness
bai14	fear of losing control	bdi14	worthlessness
bai15	difficulty in breathing	bdi15	loss of energy
bai16	fear of dying	bdi16	changes in sleeping pattern

bai17	scared	bdi17	irritability
bai18	indigestion	bdi18	changes in appetite
bai19	faint/lightheaded	bdi19	concentration difficulty
bai20	face flushed	bdi20	tiredness or fatigue
bai21	hot/cold sweats	bdi21	loss of interest in sex

Appendix 2: R Code

#Reading and Preparing the Data

```
behav.data <- read.csv("MRN.PLSCA.NegAffect.csv", header = TRUE, sep =

",", quote = "\"", dec = ".", fill = TRUE, comment.char = "")


#BAI
 #BAI1
        hist(behav.data[,37], breaks = 50, col="purple")
        BAI1.cuts <- cut(behav.data[,37],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI1.cuts)

 #BAI2
        hist(behav.data[,38], breaks = 50, col="purple")
        BAI2.cuts <- cut(behav.data[,38],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI2.cuts)

 #BAI3
        hist(behav.data[,39], breaks = 50, col="purple")
        BAI3.cuts <- cut(behav.data[,39],breaks=c(-1,0,2),
        labels=c('N','Y'))
                summary(BAI3.cuts)

 #BAI4
        hist(behav.data[,40], breaks = 50, col="purple")
#BAI4.cuts <- cut(behav.data[,40],breaks=c(-1,0,3),
```

```
        labels=c('N','Y'))
                summary(BAI4.cuts)

#BAI5
        hist(behav.data[,41], breaks = 50, col="purple")
        BAI5.cuts <- cut(behav.data[,41],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI5.cuts)

#BAI6
        hist(behav.data[,42], breaks = 50, col="purple")
        BAI6.cuts <- cut(behav.data[,42],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI6.cuts)

#BAI7
        hist(behav.data[,43], breaks = 50, col="purple")
        BAI7.cuts <- cut(behav.data[,43],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI7.cuts)

#BAI8
        hist(behav.data[,44], breaks = 50, col="purple")
        BAI8.cuts <- cut(behav.data[,44],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI8.cuts)

#BAI9
        hist(behav.data[,45], breaks = 50, col="purple")
        BAI9.cuts <- cut(behav.data[,45],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI9.cuts)

#BAI10
        hist(behav.data[,46], breaks = 50, col="purple")
        #BAI10.cuts <- cut(behav.data[,46],breaks=c(-1,0,1,3),
        #labels=c('No','Some','Yes'))
        BAI10.cuts <- cut(behav.data[,46],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI10.cuts)

#BAI11
        hist(behav.data[,47], breaks = 50, col="purple")
        BAI11.cuts <- cut(behav.data[,47],breaks=c(-1,0,3),
        labels=c('N','Y'))
                summary(BAI11.cuts)

#BAI12
        hist(behav.data[,48], breaks = 50, col="purple")
        BAI12.cuts <- cut(behav.data[,48],breaks=c(-1,0,3),
        labels=c('N','Y'))
```

```
        summary(BAI12.cuts)

#BAI13
    hist(behav.data[,49], breaks = 50, col="purple")
    BAI13.cuts <- cut(behav.data[,49],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI13.cuts)

#BAI14
    hist(behav.data[,50], breaks = 50, col="purple")
    BAI14.cuts <- cut(behav.data[,50],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI14.cuts)

#BAI15
    hist(behav.data[,51], breaks = 50, col="purple")
    BAI15.cuts <- cut(behav.data[,51],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI15.cuts)

#BAI16
    hist(behav.data[,52], breaks = 50, col="purple")
    BAI16.cuts <- cut(behav.data[,52],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI16.cuts)

#BAI17
    hist(behav.data[,53], breaks = 50, col="purple")
    BAI17.cuts <- cut(behav.data[,53],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI17.cuts)

#BAI18
#higher scores more frequent here
    hist(behav.data[,54], breaks = 50, col="purple")
    #BAI18.cuts <- cut(behav.data[,54],breaks=c(-1,0,1,3),
    #labels=c('No','Some','Yes'))
    BAI18.cuts <- cut(behav.data[,54],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI18.cuts)

#BAI19
    hist(behav.data[,55], breaks = 50, col="purple")
    BAI19.cuts <- cut(behav.data[,55],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI19.cuts)

#BAI20
    hist(behav.data[,56], breaks = 50, col="purple")
    BAI20.cuts <- cut(behav.data[,56],breaks=c(-1,0,2),
    labels=c('N','Y'))
```

```
        summary(BAI20.cuts)

#BAI21
    hist(behav.data[,57], breaks = 50, col="purple")
    BAI21.cuts <- cut(behav.data[,57],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BAI21.cuts)

#BDI
#BDI1
    hist(behav.data[,58], breaks = 50, col="purple")
    BDI1.cuts <- cut(behav.data[,58],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BDI1.cuts)
#BDI2
    hist(behav.data[,59], breaks = 50, col="purple")
    BDI2.cuts <- cut(behav.data[,59],breaks=c(-1,0,2),
    labels=c('N','Y'))
        summary(BDI2.cuts)

#BDI3
    hist(behav.data[,60], breaks = 50, col="purple")
    BDI3.cuts <- cut(behav.data[,60],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BDI3.cuts)

#BDI4
    hist(behav.data[,61], breaks = 50, col="purple")
    BDI4.cuts <- cut(behav.data[,61],breaks=c(-1,0,2),
    labels=c('N','Y'))
        summary(BDI4.cuts)

#BDI5
    hist(behav.data[,62], breaks = 50, col="purple")
    BDI5.cuts <- cut(behav.data[,62],breaks=c(-1,0,1),
    labels=c('N','Y'))
        summary(BDI5.cuts)

#BDI6
    hist(behav.data[,63], breaks = 50, col="purple")
    BDI6.cuts <- cut(behav.data[,63],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BDI6.cuts)

#BDI7
    hist(behav.data[,64], breaks = 50, col="purple")
    BDI7.cuts <- cut(behav.data[,64],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BDI7.cuts)

#BDI8
```

```
hist(behav.data[,65], breaks = 50, col="purple")
#BDI8.cuts <- cut(behav.data[,65],breaks=c(-1,0,3),
#labels=c('No','Some','Yes'))
BDI8.cuts <- cut(behav.data[,65],breaks=c(-1,0,3),
labels=c('N','Y'))
        summary(BDI8.cuts)

#BDI9
hist(behav.data[,66], breaks = 50, col="purple")
BDI9.cuts <- cut(behav.data[,66],breaks=c(-1,0,1),
labels=c('N','Y'))
        summary(BDI9.cuts)

#BDI10
hist(behav.data[,67], breaks = 50, col="purple")
BDI10.cuts <- cut(behav.data[,67],breaks=c(-1,0,4),
labels=c('N','Y'))
        summary(BDI10.cuts)

#BDI11
hist(behav.data[,68], breaks = 50, col="purple")
BDI11.cuts <- cut(behav.data[,68],breaks=c(-1,0,3),
labels=c('N','Y'))
        summary(BDI11.cuts)

#BDI12
hist(behav.data[,69], breaks = 50, col="purple")
BDI12.cuts <- cut(behav.data[,69],breaks=c(-1,0,3),
labels=c('N','Y'))
        summary(BDI12.cuts)

#BDI13
hist(behav.data[,70], breaks = 50, col="purple")
BDI13.cuts <- cut(behav.data[,70],breaks=c(-1,0,3),
labels=c('N','Y'))
        summary(BDI13.cuts)

#BDI14
hist(behav.data[,71], breaks = 50, col="purple")
BDI14.cuts <- cut(behav.data[,71],breaks=c(-1,0,2),
labels=c('N','Y'))
        summary(BDI14.cuts)

#BDI15
hist(behav.data[,72], breaks = 50, col="purple")
BDI15.cuts <- cut(behav.data[,72],breaks=c(-1,0,1),
labels=c('N','Y'))
        summary(BDI15.cuts)

#BDI16
hist(behav.data[,73], breaks = 50, col="purple")
```

```
BDI16.cuts <- cut(behav.data[,73],breaks=c(-1,0,3.5),
labels=c('N','Y'))
        summary(BDI16.cuts)

#BDI17
    hist(behav.data[,74], breaks = 50, col="purple")
    BDI17.cuts <- cut(behav.data[,74],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BDI17.cuts)

#BDI18
    hist(behav.data[,75], breaks = 50, col="purple")
    BDI18.cuts <- cut(behav.data[,75],breaks=c(-1,0,3.5),
    labels=c('N','Y'))
        summary(BDI18.cuts)

#BDI19
    hist(behav.data[,76], breaks = 50, col="purple")
    BDI19.cuts <- cut(behav.data[,76],breaks=c(-1,0,3),
    labels=c('N','Y'))
        summary(BDI19.cuts)

#BDI20
    hist(behav.data[,77], breaks = 50, col="purple")
    BDI20.cuts <- cut(behav.data[,77],breaks=c(-1,0,2),
    labels=c('N','Y'))
        summary(BDI20.cuts)

#BDI21
    hist(behav.data[,78], breaks = 50, col="purple")
    BDI21.cuts <- cut(behav.data[,78],breaks=c(-1,0,2),
    labels=c('N','Y'))
        summary(BDI21.cuts)



behav.data.nom <- cbind(
#as.character(BAItot.cuts), as.character(BDItot.cuts),
as.character(BAI1.cuts),as.character(BAI2.cuts),as.character(BAI3.cuts),
as.character(BAI4.cuts),as.character(BAI5.cuts),as.character(BAI6.cuts),
as.character(BAI7.cuts),as.character(BAI8.cuts),as.character(BAI9.cuts),
as.character(BAI10.cuts),as.character(BAI11.cuts),as.character(BAI12.cuts),
as.character(BAI13.cuts),as.character(BAI14.cuts),as.character(BAI15.cuts),
as.character(BAI16.cuts),as.character(BAI17.cuts),as.character(BAI18.cuts),
as.character(BAI19.cuts),as.character(BAI20.cuts),as.character(BAI21.cuts),

as.character(BDI1.cuts),as.character(BDI2.cuts),as.character(BDI3.cuts),
as.character(BDI4.cuts),as.character(BDI5.cuts),as.character(BDI6.cuts),
as.character(BDI7.cuts),as.character(BDI8.cuts),as.character(BDI9.cuts),
as.character(BDI10.cuts),as.character(BDI11.cuts),as.character(BDI12.cuts),
```

```
as.character(BDI13.cuts),as.character(BDI14.cuts),as.character(BDI15.cuts),
as.character(BDI16.cuts),as.character(BDI17.cuts),as.character(BDI18.cuts),
as.character(BDI19.cuts),as.character(BDI20.cuts),as.character(BDI21.cuts))

colnames(behav.data.nom) <- c(#'BAItot','BDItot',
'A1','A2','A3','A4','A5','A6','A7','A8','A9','A10','A11','A12','A13','A14','A15','A16','A17','A18','A19','A
 20','A21','D1','D2','D3','D4','D5','D6','D7','D8','D9','D10','D11','D12','D13','D14','D15','D16','D17','
 D18','D19','D20','D21')

rownames(behav.data.nom) <- behav.data[,1]
```

#Analysis: MCA

```
MJ.MCA.h <- epMCA(behav.data.nom, DESIGN = NULL, make_design_nominal = TRUE,
masses = NULL, weights = NULL,hellinger = TRUE, symmetric = FALSE, graphs = TRUE, k =
0)

MJ.MCA.h$Plotting.Data$fj.col[1:42,1] <- "orange"
MJ.MCA.h$Plotting.Data$fj.col[43:84,1] <- "dodgerblue3"


MJ.MCA.h$Plotting.Data$fi.col[1:43,1] <- "mediumpurple2"
MJ.MCA.h$Plotting.Data$fi.col[44:194,1] <- "green"
```

#Analysis: PLSCA

```
source("MRN.MCA.NegAffectOnly.R")


setwd("/Users/arielketcherside/Desktop/RMIII_Project/data/FINAL.ANALYSIS")
SNPs.data <- read.csv("SNPs.for.analysis2.csv", header = TRUE, sep = ",", quote = "\"", dec =
 ".", fill = TRUE, comment.char = "")


SNPs.small <- SNPs.data[,-1:-2]

rownames(SNPs.small) <- SNPs.data[,1]
colnames(SNPs.small) <- c("rs1049353_A", "rs6454674_G", "rs806368_C",  "rs1042713_A",
 "rs2066713_T", "rs165722_T", "rs4646312_C", "rs6311_T")

snp.data.to.replace <- SNPs.small
snp.data.to.replace <- replace(snp.data.to.replace,snp.data.to.replace==2,'aa') ##turns 2s into
 aa (minor minor)
```

```
snp.data.to.replace <- replace(snp.data.to.replace,snp.data.to.replace=='0','AA')  ##turns 0s into
 AA (major major)
snp.data.to.replace <- replace(snp.data.to.replace,snp.data.to.replace=='1','Aa')  ##turns 1s into
 aa (major minor)

SNPs <- snp.data.to.replace

Depression_Anxiety <- behav.data.nom

SNPs.nom <- makeNominalData(SNPs)
DepAnx.nom <- makeNominalData(Depression_Anxiety)


MJ.PLSCA <- tepPLSCA(Depression_Anxiety, SNPs, make_data1_nominal = TRUE,
 make_data2_nominal = TRUE,
DESIGN = NULL, make_design_nominal = TRUE,
weights1=NULL, weights2 = NULL,
symmetric = TRUE, graphs = TRUE, k = 0)


#Neg.Affect
MJ.PLSCA$Plotting.Data$fi.col[1:42,] <- "goldenrod1"
MJ.PLSCA$Plotting.Data$fii.col[1:18,] <- "dodgerblue3"
MJ.PLSCA$Plotting.Data$fii.col[19:100,] <- "forestgreen"


tepGraphs(MJ.PLSCA, DESIGN = NULL, x_axis = 1, y_axis = 2,
 fi.col = MJ.PLSCA$Plotting.Data$fi.col, fi.pch = NULL,
 fii.col = MJ.PLSCA$Plotting.Data$fii.col, fii.pch = NULL,
 fj.col = MJ.PLSCA$Plotting.Data$fj.col, fj.pch = NULL,
 col.offset = NULL, constraints = NULL, lv.constraints = NULL,
 xlab = NULL, ylab = NULL, main = NULL,
 lvPlots = TRUE, lvAgainst = TRUE,
 contributionPlots = FALSE, correlationPlotter = FALSE,
 showHulls = 1, biplots = FALSE, graphs = TRUE)
```

#Inference

```
X <- SNPs.nom
Y <- DepAnx.nom
Z <- t(X)%*%Y

chisq.test(Z, simulate.p.value = TRUE, B=1000)


source('plsc.R')

source('plsc.perm.boot.R')
```

```
 source('norm.mat.R')
 X <- makeNominalData(SNPs)
 Y <- makeNominalData(Behav.m)
perm.res <- plsc.perm.boot(X,Y)
plsc.res<- plsc(X,Y)
```

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