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Principal domains of quantitative anxiety trait in subjects with lifetime history of mania

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Abstract

Background—High commorbidity rates for anxiety have been documented in subjects with history of mania or hypomania. We explored the presence of latent constructs of quantitative anxiety in subjects who have a history of mania or hypomania.

Methods—We conducted an exploratory factor analysis of anxiety trait in 212 subjects who have a lifetime history of at least one manic/hypomanic syndrome. Participants were originally recruited for a Costa Rican sibling pair genetic study of Bipolar Disorder. We used principal factors extraction method with squared multiple correlations (SAS/SAT Professional software) of the STAI (trait subscale).

Results—A three-factor solution with a good simple structure and statistical adequacy was obtained with a KMO of 0,84 (>0.6) and Bartlett's Test of Sphericity of 2,4668E-162 ($p<0.05$). Items grouped into anxiety-absent factor and the anxiety-present symptoms in two additional factors based on the nature of the symptoms, worry and rumination.

Limitations—Comorbid disorders could affect the interaction of anxiety score with manic/hypomanic symptoms. Some statistical parameters (mood status independence, score distribution and correlation between trait score and quantitative mania/hypomania) were not taking in consideration to extract the factors. Because anxiety dimensions were explored on individuals with history of mania or hypomania and not in healthy subjects, comparison of our results with other studies can draw confusing conclusions.

Conclusions—Two underlying constructs, worry and rumination may explain anxiety sub-syndromic symptoms in Costa Rican patients with history of mania or hypomania.

Keywords

Mania; Hypomania; Exploratory factor analysis; Family studies; Sub-syndromic anxiety

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1. Introduction

Current diagnostic systems do not adequately reflect the complexity of bipolar disorder (BD) (Akiskal and Pinto, 1999; Akiskal et al., 2000). Categorical diagnosis and global severity assessments provide suboptimal information to improve our knowledge on pathophysiology, diagnostic assessment, prognosis, and novel therapies. Insights into BP genetics, illness course and pharmacological studies increasingly reinforce this conclusion. Syndromal diagnostic criteria could also be aided by the reliable convergence of several dimensional variables, including behavioral domains, illness course and family history (Goodwin and Jamison, 2007; Vieta and Phillips, 2007; Contreras et al., 2010).

High commorbidity rates for anxiety have been documented in bipolar I disorder (MacKinnon et al., 2002; McElroy et al., 2001). However, sub-syndromal levels of anxiety have also been associated with bipolar I patients who did not meet criteria for a categorical Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) anxiety disorder (Mantere et al., 2008). Research on the underlying variables and factors is limited to individual categorical clinical states (Sato et al., 2002). The above limitations have made it difficult to extrapolate results to current clinical practices and to replicate findings.

Clinical and epidemiologic evidence suggests that major mood disorders form a spectrum from major depressive disorder to pure mania (Angst et al., 2010). More specifically, transient manic symptoms in children were probed to be a risk factor for eventual conversion to the bipolar spectrum disorder (Nadkarni and Fristad, 2010). Family studies have also supported the concept of a spectrum of subthreshold affective traits or temperaments (e.g. ciclothymia and anxiety) in bipolar pedigrees (Vázquez et al., 2008). Since the concept of bipolar spectrum denotes overlapping clinical expressions, without necessarily implying underlying genetic homogeneity; we arbitrarily defined bipolar spectrum disorder as lifetime history of any manic syndrome/episode. Thus, we analyzed subjects who have a history of mania or hypomania (bipolar disorder type I, bipolar disorder type II, bipolar disorder not otherwise specified, schizoaffective bipolar disorder, schizophrenia with manic syndrome and substance related manic syndrome). One of the reasons for using any manic or hypomanic syndrome as inclusion criteria is the fact that in our previous published work the trait score was correlated with lifetime mania (LDPS M-1 duration x severity) ($p<.0001$) after controlling for age and gender. In that study we did not find significant correlation between anxiety trait and depression (Contreras et al., 2010).

The goal of this study was to explore the presence of latent constructs which contribute to the STAI score in subjects who have a history of mania. We used the anxiety trait (trait subscale of the STAI) that showed normal distribution in healthy subjects, significant heritability and genetic correlation and independence to mood clinical state in our multiplex bipolar I families (Contreras et al., 2010). Also, research has shown that state-trait dimensions (from studying the two subscales together) may be multidimensional themselves (Virella et al., 1994). The advantage of knowing if there are factors is to better understand the biologic components which make up the global STAI score in this group of patients. If this anxiety trait represents a biological marker for bipolar I disorder in this Costa Rican sample, exploration of its underlying constructs might provide a high face and construct validity with respect to mania/hypomania in this Costa Rican sample.

We reasoned that the combination of quantitative anxiety trait and best estimation diagnostic process based on DSM-IV diagnostic criteria would serve to yield reliable and informative scores on fundamental affect components of subjects with history of mania/hypomania.

2. Methods

2.1. Participants

Subjects were originally recruited for a multi-site bipolar sibling pair study (Genetics of Bipolar disorder in Latino Populations NIMH 1 R01 MH069856-01A2). The study was explained to each subject and written informed consent was obtained. This study was reviewed and approved by the Institutional Review Boards of the University of Costa Rica and the University of Texas (UTHSCSA). The sample was composed of 212 subjects. Each individual had lifetime history of at least one manic/hypomanic syndrome.

2.2 Diagnostic assessment

The subjects were diagnosed based on the diagnostic criteria of DSM-IV through a best estimation process utilizing clinical information obtained from the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), a Family Interview for Genetic Studies (Maxwell, 1992) and psychiatric records. Final diagnoses were determined through a consensus process where two independent psychiatrists reviewed all available information and arrived at independent diagnoses.

2.3 Anxiety assessment

Sub-syndromal anxiety was assessed by means of the STAI to measure anxiety scores in each individual. The STAI is a self-rated instrument that contains two 20-item scales (4 response choices per item, higher scores indicate higher anxiety) (Spielberger et al., 1983). One scale measures state anxiety (i.e. the extent to which respondents experience anxiety symptoms at the time of measurement) (Vigneau and Cormier, 2008). The second scale measures trait anxiety (i.e. the extent to which respondents generally experience anxiety symptoms). This instrument has been validated in Spanish (Rodrigo and Lusiardo, 1988).

2.1 Exploratory factor analysis

Exploratory factor analysis was performed using the principal factors extraction method with squared multiple correlations (SMC) of each variable with all the other variables for the prior communality estimates. This is the simplest and computationally most efficient method of common factor analysis. Although maximum likelihood (ML) factor analysis has desirable asymptotic properties and allows to test hypotheses about the number of common factors, it generates better estimates in samples larger than the number of subject of the current study (Joreskog, 1977).

To determine whether the common factor model is appropriate, we calculated the Kaiser's measure of sampling adequacy (KMO). This measure varies between 0 and 1; a value greater than 0.6 was considered the minimum accepted value (Kaiser, 1974). Bartlett's Test of Sphericity tests the null hypothesis: that the correlation matrix is an identity matrix (matrix in which all of the diagonal elements are 1 and all off diagonal elements are 0). By using the test, the null hypothesis would be rejected.

Partial correlation (controlling all other variables) was explored to evaluate whether the data was appropriate for the factor model. It is presumed that partial correlation will be small compared to the original correlations. SMC replaces the diagonal of the original observed correlation matrix by these square multiple correlations.

During the extraction, the values indicate the proportion of each variable's variance that can be explained by the retained factors. Variables with high values are well represented in the common factor space, while variables with low values are not well represented. Because the square multiple correlations are usually less than one, the resulting correlation matrix for

factoring is called the reduced correlation matrix. The Regression Method was used to produce the coefficients for each item in order to generate the estimated factor scores for each observation (SAS/SAT Professional software, SAS Institute, Inc., Cary, NC). The initial Eigenvalues are the variances of the factors. The first factor accounts for the most variance (and hence have the highest eigenvalue), and the next factor will account for as much of the left over variance as it can. Thus, each successive factor will account for less and less variance. The percentage of variance contains the percent of total variance accounted for by each factor (its cumulative contains the cumulative percentage of variance accounted for by the current and all preceding factors). To determine the optimal number of factors to be extracted, the protocol required each factor to have at least four items with rotated factor loading scores greater than 0.30. This cut-off score was chosen because it does not eliminate potentially significant factors and it conforms to traditional exploratory factor analysis methodology (Floyd and Widaman, 1995). The scree plot produces a plot of the eigenvalues that is helpful in deciding how many factors to use (Fabrigar et al., 1999).

The Extraction Sums of Squared Loadings correspond to the number of factors retained. The rotation sums of squared loadings represent the distribution of the variance after the varimax rotation. Varimax rotation maximizes the variance of each of the factors, so the total amount of variance accounted for is redistributed over the three extracted factors (Kaiser, 1960). Rotation of factor pattern is to apply a nonsingular linear transformation to the unrotated factor pattern matrix. An optimal transformation is usually defined as a minimum or maximum point of a simplicity function. Different rotation methods are based on different simplicity functions employed. Since orthogonal rotation of the extracted factor loadings was conducted we were not able to explore whether the obtained factors were correlated.

Results

3.1 Sample characteristics

Out of the 212 subjects, 164 (77%) had bipolar disorder type I, 8 (4%) bipolar disorder type II, 18 (8%) bipolar disorder not otherwise specified, 13 (6%) schizoaffective disorder bipolar type, 2 (1%) schizophrenia with manic syndrome, 7 (4%) substance induced mood disorder with manic symptoms. One-hundred and fifteen subjects (54%) were females and the average age of the whole sample was 45.3 (SD=12.2). The sample of this analysis was composed of 68 families (average number of individuals per family 3 members, range: 1-9).

3.2 Factor structure

To assess if the common factor model was appropriate for our sample, the correlation matrix of the STAI trait subscale (20 items) was computed. Inspection of the correlation matrix showed that the correlations were substantial, indicating the presence of a substantial general factor. KMO of 0,845275243 (>0.6) and Bartlett's Test of Sphericity of 2,4668E-162 ($p<0.05$) showed adequacy of data for factor analysis. Since the aim of this work was exploratory factor analysis in pedigrees with one or more affected members, factor scores were not computed which are necessary for heritability estimates as an index of familiarity within this sample.

After computing the prior communality estimates (proportion of variance of each of the 20 items shared by all remaining items) we found that item 11 (I am inclined to take things hard) has the prior communality estimate of 0.26, which means that only 26% of the variance of the item 11 is shared by all other items, indicating that this item is somehow a different construct than the other items. A similar situation is shown with item 14 (I try to avoid facing facing a crisis or difficulty). Since more common communalities in social

sciences are low to moderate (0.40-0.70) (Velicer and Fava, 1998), items with communalities less than 0.40 were not included in the current analysis.

As shown in table 2, the sum of all prior communality estimates, 9.96 (the estimate of the common variance among all items) constitutes about 50% of the total variance present among all 20 items, current estimate of the common variance was slightly larger (10.20). According to the proportion criterion (>0.30) and the scree plot (not shown) three factors can be retained. For the scree plot, a point below which factors explain relatively little variance and above which they explain substantially more is shown as an “elbow”. Cattell’s guidelines (Cattell, 1966) call for retaining factors above the elbow and rejecting those below it.

We analyzed the item loading table after rotation to select the “cleanest” factor structure: item loadings above 0.30, no items crossloadings, and no factor with fewer than three items.

The off-diagonal elements of the residual correlation matrix (table not shown) are close to 0.01, indicating that the correlations among the 20 items can be accurately reproduced from the retained factors. The root mean squared off-diagonal residual is 0.03. The inspection of the partial correlation matrix yields similar results: the correlations among the 20 items after the retained factors are accounted for are all close to zero. The root mean squared partial correlation is 0.06, indicating that four latent factors can accurately account for the observed correlations among the 20 items.

Based on the obtained factor pattern all variables except item 11 and 14 had high loadings on one factor and became easier to interpret after rotation. As seen in table 1, 16 items had factor loadings ranging from 0.52 to 0.75. No item had a loading greater than 0.50 on more than one factor. Items Q1 (I feel pleasant), Q6 (I feel rested), Q7 (I am calm and cool), Q10 (I am happy), Q13 (I feel secure), Q16 (I am content) and Q19 (I am a steady person) load higher on Factor1. Items Q2 (I tire quickly), Q3 (I feel like crying), Q9 (I worry too much over something that really doesn’t matter) and Q20 (I get in a state of tension or turmoil as I think over my recent concerns and interests) load higher on Factor2. Items Q5 (I am losing out of things because I can’t make up my mind soon enough), Q8 (I feel that difficulties are piling up so that I cannot overcome them), Q12 (I lack self-confidence), Q17 (Some unimportant thought runs through my mind and bothers me) and Q18 (I take disappointments so keenly that I can’t put them out of my mind) load higher on Factor3.

The proportion of variance explained by each factor after rotation is shown in table 2. Even though the variance explained by the rotated Factor1 is less than that explained by the unrotated factor, the cumulative variance explained by both common factors remains the same after the orthogonal rotation.

3. Discussion

Bipolar patients with high anxiety rates have longer, more frequent and more difficult to treat mood episodes; they also show greater functional impairment, greater substance abuse, and earlier onset of mood illness (Feske et al., 2000; Frank et al., 2002; Otto et al., 2006). Additionally, adequate treatment of comorbid anxiety has been suggested to reduce the risk for the development of substance use disorder in patients with BP (Gao et al., 2010). Milder anxiety phenotypes such as anxious temperament (increased behavioral and physiological reactivity to mildly threatening stimuli) have also been documented not only in humans but also in primates (Fox et al., 2010). These anxiety-related symptoms can be measured as quantitative traits using the STAI for refining clinical phenotypes as done in our previous publication. The purpose of the current study was to explore underlying structure of the STAI trait score in individuals with history of mania/hypomania.

The exploratory factor analyses suggested that three-factor solution was meaningful and had good simple structure. The composition of items combined the anxiety-absent items in one factor and the anxiety-present symptoms in two additional factors based on the nature of the symptoms, worry and rumination. This factor solution was consistent with previous studies with the English version of the STAI that have also reported three-factor solutions in which State and Trait anxiety-absent and anxiety-present items loaded (0.30 or above) on different factors (Barker et al., 1977).

Worry and rumination are cognitive processes that impact on the experience of anxious and mood symptoms. Individuals with anxious temperament are maladaptively shy and chronically suffer from worry and apprehension. In a study conducted on students, Ryan (2007) found that worry was associated with anxious and depressive symptoms whereas rumination was uniquely related to depression. In comparison to rumination, worry emerged as the dominant cognitive vulnerability factor that predicted increments in symptoms over time. Some of these results were replicated by Segerstrom et al. (2000) who found that individuals with repetitive thought show maintenance of anxious symptoms and proposed that failures of this emotional processing may lead to repetitive thought which increases negative mood states. It is expected that clinical manifestation of mood episodes in our subjects are more difficult to treat depending on the presence of anxiety symptoms (e.g. worry and rumination). How the type of symptoms affects the clinical presentation and prognosis of the mania/hypomania raise an important line of research. Furthermore, Gruber et al. (2008) examined bipolar I patients, individuals with insomnia and a non clinical control group. Rumination and worry were endorsed to a larger degree by the bipolar and insomnia groups compared to the control group. Different to the study conducted by Gruber et al. (2008) our sample was composed by bipolar type I, bipolar type II, schizoaffective bipolar disorder, schizophrenia with manic syndrome and substance related manic syndrome). We were able to partially replicate their results by extracting two of their same factors (worry and rumination).

Researchers have begun to document the presence of worry in bipolar disorder where comorbidity may be a link between temperament and genotype across the main diagnosis and also as the same continuum of severity. Worry and rumination as a phenotypic characterization may assist in genotyping; however, its predictive value on actual illness outcome still requires more research. Our proposed underlying structure of subsyndromal anxiety in individuals with history of mania/hypomania should be considered as an important factor in defining better phenotypic characterizations on a broader diagnostic concept. These results are in accordance to the definition of what today it is considered bipolar disorder type II (i.e. cyclothymic reactivity, neurotic features and panic attacks) (Akiskal et al., 2006).

According to Cloninger's seven-factor biosocial model of personality, harm avoidance is a trait leading to behaviors that avoid aversive stimuli (Cloninger et al., 1994). The four harm avoidance subscales includes: anticipatory worry, fear of uncertainty, shyness and fatigability. High harm avoidance has been the most consistent finding across bipolar studies and it has been shown to be vulnerable to state effects (Engstrom et al., 2004) being more associated with the subsyndromal depression experienced by many patients in interepisode periods (Judd et al., 2002). On the other hand, research has shown that patients with anxiety disorders have higher scores on harm avoidance compared with healthy individuals (Ball et al., 2002). Worriers have less perceived control over their anxiety, their inner experience of emotions, and less control over the external signs of emotion (Gould and Edelstein, 2010). In our study the following items were identified in factor 2: Q2 I tire quickly, Q3 I feel like crying, Q9 I worry too much over something that really doesn't matter and Q20 I get in a state of tension or turmoil as I think over my recent concerns and interests. It has been found

that rumination is associated with hypomania scores. Rusting and Nolen-Hoeksemad, (1998) found that rumination increases anger and two years later Nolen-Hoeksema (2000) found that rumination increases anxiety. Additionally, bipolar remitted patients have reported greater rumination than those in acute mood episode (Thomas et al., 2007). Being these items very similar to those of the harm avoidance subscale, our findings suggest that harm avoidance, as proposed by Cloninger, somehow defines a specific anxiety dimension of our sample. In the specific case of our study, we called this anxiety dimension as worry considering it the most appropriate term to define this group of anxiety symptoms.

Comorbid obsessive compulsive disorder in bipolar disorder is characterized by episodic course, higher rates of certain obsessions (e.g. aggressive/impulsive, sexual, religious, and obsessional doubts) which require more frequent hospitalizations and complex pharmacological interventions (Perugi et al., 2002). A defining characteristic of OCD is unsuccessful suppression of unwanted thoughts. Obsessive symptoms have else been positively associated with rumination and inversely associated with perceived thought control ability (Grisham and Williams, 2009). Rumination involves repetitive thought about past events, current mood states, or failure to achieve goals (Martin and Tesser, 1996). Evidence suggests that rumination predicts the future occurrence of anxiety in anxious depressed comorbid conditions (Nolen-Hoeksema, 2000). In subjects with history of mania/hypomania, rumination may play an important role in triggering depressive episodes too. In our study, the following items were grouped in factor 3: Q5 I am losing out of things because I can't make up my mind soon enough, Q8 I feel that difficulties are piling up so that I cannot overcome them, Q12 I lack self-confidence, Q17 some unimportant thought runs through my mind and bothers me and Q18 I take disappointments so keenly that I can't put them out of my mind. Due to the nature of the items we called this factor as rumination. One can argue that low-confidence represents a distinct type of anxiety; however rumination exhibits a negative effect on individual's decision-making which can ultimately be addressed as low self confidence. For instance, Van Randenborgh et al studied the underlying mechanisms of rumination in dysphoric and nondysphoric subjects. They found that dysphoric subjects experience the decisions as more difficult and have less confidence in their choices (van Randenborgh et al., 2010).

Our results can help to develop further animal research models to study the underlying etiologies of anxious-related processes in patients with history of mania/hypomania. Mounting evidence shows some functional genetic variants associated with anxiety giving new insights into the molecular genetic mechanisms underlying these disorders. Specifically, a study assessing sustained trait-like brain responses associated with anxious temperament rhesus monkeys found significant heritability of the anxious temperament phenotype (using quantitative genetic analysis) and the metabolic activity in anxious temperament-associated hippocampal regions (using voxelwise analyses) (Oler et al., 2010). Recent findings from a study using a knock-in mouse design suggested that subjects homozygous for the 66Met allele scored significantly higher than Val66 allele carriers on anxiety-related facets of the construct 'harm avoidance' (i.e., 'anticipatory worry' and 'fear of uncertainty') of the Temperament and Character Inventory (Montag et al., 2010). Somerville et al. (2010) found that bed nucleus of the stria terminalis showed greater overall recruitment and exaggerated tracking of threat proximity in individuals with greater anxiety. These results suggest continuous functional magnetic resonance imaging could be used for elucidating the neural circuitries underlying sustained anticipatory features that ultimately might be utilized in individuals with history of mania/hypomania.

In conclusion, our exploration analysis of anxiety subsyndromic symptoms has identified two anxiety constructs, worry and rumination. Based on the reviewed literature and on our results, it seems that worry and rumination are common anxiety dimensions across patients

with any history of mania/hypomania and not only in bipolar disorder type I. Both, worry about potential future events and rumination about recently past events may play a causal role in the creation of anxious comorbid disorders (as categorical diagnosis) in this group of patients. The exploration of these underlying constructs will yield our proposed endophenotype of high face and construct validity with respect to subsyndromic anxiety. Our next step will be based on confirmatory factor analysis as well as other latent variable modeling techniques to test hypotheses via inferential approach. We will test the obtained factors and analyze the variation among variables using the few newly created variables (factors) and their meaning based on current literature. Further research will test whether these component factor scores are heritable, whether they share the same genetic factors, which (if they are not highly correlated) may further help define the components underlying bipolar disorder and other psychiatric disorders with a history of mania/hypomania. We will focus on aetiological validity of these factors where quantitative anxiety trait can be used to identify genetic loci and genes which underlie this “portion” of the complex phenotype of patients with history of mania/hypomania in the isolated Costa Rican sample. Our line of research intents to improve our understanding on the pathophysiology of affective and anxiety disorders for a better diagnostic and pharmacologic treatment of these disabling disorders.

Some limitations of the current study are the assumption of the same statistical parameters from our previous work (no significant differences in the trait score regarding mood current status, normal distribution of trait score and positive correlation between trait score and quantitative mania/hypomania). Even though the number of individuals are similar and belong to the same original study following identical recruitment and diagnostic process, the inclusion criteria differs due to specific research question. Previously, we analyzed 30 bipolar I extended families (300 subjects) and 20 healthy unrelated controls to study anxiety as a candidate endophenotype for the Costa Rican bipolar I sample. In the current work we conducted an exploratory factor analysis of subjects who have history of mania/hypomania without taking in consideration familiarity. Confirmatory factor analysis is beyond the scope of the current work and therefore drawing substantive conclusions should be cautiously taken. For instance, for a given sample made up of pedigrees of related individuals, the variance of the trait should be partied into factors that reflect (depending on model specification) additive polygenic effects vs sibship effects or nuclear family effects. The effects of those factors could be assessed after obtaining factor scores with confirmatory factor analysis and estimating heritability as an index of familiality. Even though this analysis was conducted with a small sample size, studies have revealed that adequate sample size in factor analysis is determined by the nature of the data (MacCallum et al., 1999). Our data showed uniformly high communalities without cross loadings and more than three variables loading strongly on each retained factor. Since most of the psychometric analyses of this scale have been conducted on nonclinical sample, comparison of our results with other studies becomes an important limitation.

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Table 1

Factors Loadings (Exploratory VARIMAX Factor Analysis):

Anxiety symptoms	Factor 1 (Anxiety-absent)	Factor 2 (Worry)	Factor 3 (Rumination)
I feel pleasant	**0.73660**	−0.16663	0.06521
I feel rested	**0.62607**	−0.01220	−0.06915
I am calm and cool	**0.65587**	−0.11590	0.11569
I am happy	**0.69437**	−0.16536	0.00669
I feel secure	**0.74675**	−0.00832	−0.19510
I am content	**0.73103**	−0.07335	−0.21984
I am a steady person	**0.69199**	−0.20100	−0.03862
I tire quickly	−0.18017	**0.74615**	0.07403
I feel like crying	−0.16474	**0.75250**	0.25264
I worry too much over something that really doesn't matter	−0.18107	**0.72997**	0.26173
I get in a state of tension or turmoil as I think over my recent concerns and interests	−0.19335	**0.67330**	0.29544
I am losing out of things because I can't make up my mind soon enough	0.02293	0.49221	**0.54757**
I feel that difficulties are piling up so that I cannot overcome them	−0.08255	0.23013	**0.52291**
I lack self-confidence	−0.10866	0.44104	**0.52853**
Some unimportant thought runs through my mind and bothers me	−0.14049	0.46897	**0.56760**
I take disappointments so keenly that I can't put them out of my mind	−0.21004	0.28569	**0.63162**

Table 2

Variance Explained by Each Factor

	Factor 1	Factor 2	Factor 3	Communality
Before rotation	5.9955264	2.8768772	0.9096455	9.96186083
After rotation	3.7367315	3.4475323	2.5384521	10.202708