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Exploring the boundary between temperament and generalized anxiety disorder: A receiver operating characteristic analysis

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Abstract

Studies of individuals with an increased tendency to experience negative emotions such as fear, sadness, and anger have documented links between this temperamental trait and anxiety disorders. There exists debate, however, concerning the degree to which high levels of a temperamental trait are a necessary and/or sufficient component of a DSM diagnosis. In this study, receiver operating characteristic (ROC) analyses assessed the relations between levels of harm avoidance (HA) and generalized anxiety disorder (GAD) diagnoses in 334 children and their parents. Analyses revealed HA scores to be highly predictive of GAD diagnoses in children ($AUC = .791, P < .001$) and adults ($AUC = .818, P < .001$). However, there were many individuals with high HA scores who did not qualify for a GAD diagnosis. These findings suggest that while there are strong associations between HA and GAD, high levels of HA are neither necessary nor sufficient in the formation of clinically significant anxiety symptoms.

Keywords

Temperament; Personality; Anxiety; Generalized anxiety disorder; Children

1. Introduction

The interface between temperament and psychopathology has received increased interest of late as researchers continue to find strong links between temperamental traits and a wide array of psychiatric disorders (Nigg & Goldsmith, 1998; Rettew & McKee, 2005). The degree of association has stirred both methodological and theoretical debate about the distinction between these supposedly independent domains (Frick, 2004). Complicating matters further is the fact that the definition of temperament remains somewhat elusive (Rothbart, 2004), although there is at least some consensus that temperament refers to individual differences in emotional reactivity and regulation that can be observed early, are moderately stable, and under at least some genetic influence (Goldsmith et al., 1987).

Some researchers have postulated temperament as a subclinical variant of psychiatric disorders (von Zerssen & Akiskal, 1998) with temperament and corresponding psychopathology existing along a single continuum (Carey, 1999; Graham & Stevenson, 1987). Under this view, more extreme levels of a particular temperamental trait would be a necessary although not sufficient element of a corresponding psychiatric disorder. A large twin study conducted in Australia (Jardine, Martin, & Henderson, 1984) reported the genetic correlation between neuroticism and anxiety to be approximately .8. Hettema, Prescott, and

Kendler (2004) recently found evidence that not only is there a high degree of correlation between neuroticism and generalized anxiety disorder (GAD) but that the two conditions may involve some of the same genes. Others, however, view temperamental dimensions as one of many risk factors for later psychopathology (Schwartz, Snidman, & Kagan, 1999) and something qualitatively distinct between psychopathology itself.

Anxiety disorders have been particularly linked to temperamental dimensions. Kagan (1994) and coworkers have proposed the temperamental dimension of behavior inhibition (BI) to describe children who become overly fearful and reticent when confronted with novel situations and people. BI as a toddler has been found to predict later psychopathology, particularly anxiety disorders (Biederman et al., 1993; Schwartz et al., 1999). Other measures of related temperamental or personality traits, variably named neuroticism, negative affectivity, or negative emotionality have also been found to have strong associations with anxiety disorders (Anthony, Lonigan, Hooe, & Phillips, 2002; Caspi, 2000; Kuo, Chih, Soong, Yang, & Chen, 2004). Using Cloninger's framework, the related dimension of harm avoidance (HA) appears to be strongly linked to many anxiety and affective disorders in both children and adults (Öngür, Farabaugh, Iosifescu, Perlis, & Fava, 2005; Pelissolo et al., 2002; Rettew, Copeland, Stanger, & Hudziak, 2004).

Many hypotheses concerning the temperament/psychopathology boundary are now able to be tested and quantified using modern data analytic techniques. One type of analysis that holds promise in quantifying the relations between two variables is receiver operating characteristic (ROC) analysis. This procedure has typically been applied to quantifying the association between a continuous test variable and a binary outcome variable at varying cut-off points of the test variable. ROC analyses allow the investigator not only to calculate the sensitivity and specificity of the test variable at different cut-off levels but also an overall area under the curve (AUC): a more general measure of the ability to optimize both sensitivity and specificity at each point of the test variable.

Williamson and colleagues (2005) performed ROC analyses in adults using a composite measure from multiple questionnaires, including the neuroticism scale from the Eysenck Personality Questionnaire (EPQ-N; Eysenck, Eysenck, & Barrett, 1985), to predict the presence of a mood or anxiety disorder, as determined through a telephone structured interview. The AUC for this composite measure was found to be good (.869), and the authors concluded that neuroticism represents a vulnerability factor for later depressive and anxiety disorders.

The goal of this study was to provide a quantitative evaluation of the degree of overlap between the temperamental trait of harm avoidance and generalized anxiety disorder in both children and adults. GAD is a highly distressing disorder characterized by chronic, excessive worry surrounding various aspects of one's life. The HA dimension was chosen because of its previously mentioned links particularly with mood and anxiety disorders, although other temperament dimensions such as low novelty seeking and reward dependence have also been implicated (Öngür et al., 2005; Pelissolo et al., 2002). Both HA and GAD share features of feeling habitually tense and worried.

While we expected a high degree of overlap, we were particularly interested to investigate the degree to which temperamental traits can exist without a psychiatric disorder and vice versa. To improve validity of both temperament and diagnosis, this study utilizes a multiple informant approach. We hypothesized that although HA scores would be highly predictive of GAD, there would be many individual cases in which high HA scores were not associated with GAD. Alternately, we expected some cases in which an individual with GAD had low or moderate HA scores. We expected, however, that the former case (tested as a sensitivity

question) would be more common than the latter (tested as a specificity question). In other words, we predicted that it would be more common for an individual to express high levels of harm avoidance in the absence of GAD relative to the existence of individuals with GAD expressing low levels of harm avoidance. Support for these hypotheses would be expected to challenge the theory that a clinical diagnosis of GAD belongs to a fundamental continuum of neurotic temperament. To our knowledge, this is the first application of this statistical procedure to the overlap between temperament and psychopathology in a sample that includes children and adolescents.

2. Methods

2.1. Subjects

2.1.1. Subject recruitment—Participants came from a family study conducted in the northeastern United States that was designed to examine the genetic and environmental contributions to attention and aggression. Details of the study design are presented elsewhere (Hudziak, Copeland, Stanger, & Wadsworth, 2004); however, we will summarize some of the procedures. Potential families were recruited from local pediatricians and psychiatrists in a university-based outpatient clinic based on a review of clinical records. Local newspaper advertisements and posters were also used. Families were initially screened over the telephone for the following demographic inclusion criteria: (1) proband child between the ages of 6 and 18; (2) proband child living with at least one biological parent; and (3) proband child with at least one sibling between the ages of 6 and 18. If a family met those requirements, they were then sent parent-rater Child Behavior Checklists (Achenbach, 1991) to assess levels of behavior problems. Four target groups of probands were sought based on the CBCL, including subjects with (1) T scores greater than 67 on the attention problems (AP) scale and less than 60 on the aggressive behavior (AG) scale; (2) T scores greater than 67 on AG but less than 60 on AP; (3) T scores greater than 67 on both scales; and (4) T scores less than 60 on both scales. Siblings were not subject to any of the T score restrictions placed on probands.

A total of 206 families were recruited into the family study. From these families, there were 458 children (195 girls, 263 boys); 197 mothers, and 101 fathers who agreed to participate in the study. The sample was almost exclusively Caucasian with an average score of 6.38 (S.D. = 2.15) on the Hollinghead SES scale (Hollinghead, 1975).

2.2. Procedures

2.2.1. Diagnostic assessment—Families participated in a 2-hour visit which took place either at the research center or their home. Diagnostic data were obtained using the Vermont Structured Diagnostic Interview (Hudziak et al., 1993) a structured clinical interview modified for DSM-IV (American Psychiatric Association, 1994) in which mothers and fathers reported on symptoms for their children. Subjects 12 and over also reported on their own symptoms in a separate interview. Interviews were performed by trained interviewers and supervised by a board certified child psychiatrist. The psychometric properties of this interview are described elsewhere (Hudziak et al., 2004). Test-retest reliability was found to be good, especially for internalizing disorders, and the mean kappa for the GAD diagnosis was .88. A diagnosis of GAD was considered positive in children aged 12 and over if either the mother or child reported symptoms meeting DSM-IV criteria. This procedure is commonly used in previous research in child anxiety disorders (Foley et al., 2004). For children under age 12, we relied on maternal report only. If a child aged 12 or older only had data from one source, the data were not used for this study. Since only a limited number of fathers participated, we did not introduce the potential bias of having higher rates of

perceived GAD in families where a father also participated in the diagnostic process. For adult diagnoses, we used the VSDI conducted individually with each parent.

2.2.2. Temperament assessment—Temperament was assessed using the Temperament and Character Inventory (Cloninger, Przybeck, Svrakic, & Wetzel, 1994; Cloninger, Svrakic, & Przybeck, 1993) and its downward extension, the Junior Temperament and Character Inventory (JTICI) which has shown good reliability and validity (Luby, Svrakic, McCallum, Przybeck, & Cloninger, 1999; Lyoo et al., 2004). The JTICI, which was used to evaluate child temperament, consists of 108 statements that the respondent rates as true or false based on how the person usually acts and feels. The short form of the TCI is a 125 item self-report instrument that is widely used and that has established reliability and validity (Cloninger et al., 1994).

Only scores obtained on the harm avoidance dimension, one of the four temperament dimensions in addition to novelty seeking, reward dependence, and persistence, were considered in the present analysis. The harm avoidance dimension is a 22-item scale which includes items related to shyness, fatigability, and anticipatory worry, e.g., “My child worries more than others that bad things will happen.” Previous research has demonstrated significant correlations with other similar dimensions such as neuroticism (Kuo et al., 2004), although some discontinuities do exist (Heath, Cloninger, & Martin, 1994).

2.2.3. Use of multiple informants—Each child at least 11 years old in the study could have his or her temperament rated by up to four informants (mother, father, self, teacher). Children under 11 years old did not complete the self-report form. A composite harm avoidance score for each child was computed by averaging the score from all informants and will be described in more detail. Adult harm avoidance scores were computed from the self-report only.

2.3. Data analysis

2.3.1. Receiver operating characteristic (ROC)—Receiver operating characteristic analyses were conducted to assess the degree to which HA scores predict GAD diagnosis. ROC analyses are most commonly used to assess the prognostic capacity of a test. On the ROC graph, the sensitivity of scores is located on the Y-axis, while the 1—specificity of scores is represented on the X-axis. The curve of the graph marks the levels of specificity and sensitivity of specific cut-off scores. The area under the curve provides the probability that one can correctly identify the diagnostic status of two randomly selected subjects, where one subject meets criteria for diagnosis and one does not. AUC values obtained through ROC analysis can vary from 0.500 (correct classification of a subject occurs 50%) of the time to 1.000 (correct classification occurs every time). Determining what AUC values are suitable to use for screening varies among diagnoses and among characteristics of the sample being analyzed.

3. Results

3.1. Sample characteristics and comparisons

Two hundred and thirty one (63 fathers and 168 mothers) of a possible 298 parents (77.5%) provided sufficient temperament and diagnostic information to be included in analysis. There were no significant differences in age, sex, or SES between adults who did provide sufficient data for inclusion and those who did not. Of the possible 458 children under 18 years old in this sample, valid data including at least one informant for temperament, and diagnostic data (GAD) were available for 334 (73.0%) children (135 girls, 199 boys). There were no differences with regard to sex, age, SES, or total problems of the CBCL between

subjects who had valid data for both diagnosis and temperament and those who did not, with the exception that the children with missing data were older (12.19 years vs. 10.44 years; $t(451) = 5.81, P < .001$). In the child sample, there were 62 children with only 1 informant for temperament (usually mother), 150 with 2 informants, 104 with 3 informants and 8 with 4 informants. Using analysis of variance procedures, there were no differences in mean HA scores or total problems on the CBCL by number of informants. Demographic and comorbidity data are presented in Table 1.

3.2. Child harm avoidance scores and GAD diagnosis

Analyses were initially conducted separately for the proband ($n = 147$) and sibling ($n = 187$) groups as well as for males and females. We also analyzed different configurations of informants (e.g., basing GAD diagnosis on mother report only). Since there were no significant differences in the ROC curves based on the 95% confidence interval, we combined probands and siblings and combined genders for both adults and children. Data are thus presented for two groups, children and adults.

Mean composite harm avoidance scores for child participants were 8.66 (S.D. = 4.34) and ranged from 0 to 20.50. Forty-one (12.3%) were identified as having a current diagnosis of GAD. ROC analysis tested the extent to which mean harm avoidance scores predicted GAD diagnosis. The sensitivity and specificity data are presented in Table 2. A sensitivity of 90% (ability to correctly predict GAD based on HA scores) was achieved with a composite cut-off score of 6.40. This 90% cut-off is less than the mean score, suggesting that using HA scores as a test would result in many false positives unless a very low cut-off score was used. At this cut-off, the specificity was 39%. On the other hand, a 90% specificity rate is achieved at a score of 13.83, where the sensitivity is 44%. As shown in Fig. 1, the analysis revealed an acceptable AUC of .791 (95% CI .716–.866) in the prediction of GAD from mean harm avoidance scores, which was significantly different from the random predictor ($AUC = .500, P < .001$) and suggested a significant degree of overlap between HA and GAD.

Fig. 2 displays qualitatively the distribution of composite child HA scores and those who met criteria for GAD. Results clearly show a preponderance of GAD diagnosis towards the higher range of HA scores; however, there are a number of exceptions. In particular, the graph reveals a number of children with high HA scores and no GAD. Of the 33 children with HA scores more than 1.5 standard deviations above the mean, 14 (42%) had GAD. For the 10 children more than 2 standard deviations above the mean, half had a GAD diagnosis. From the other perspective, only 7 of the 41 children with GAD (17%) had HA scores below the mean and only 1 had a score less than 1 standard deviation below the mean.

3.3. Parental harm avoidance scores and GAD diagnosis

Parent self-report harm avoidance scores ranged from .00 to 20.00 with a mean of 8.59 (S.D. = 4.26). Sensitivity and specificity data are presented in Table 2. Twenty-seven of 231 parents (11.7%) identified themselves as having a diagnosis of GAD. ROC analysis revealed a good AUC of .818 in the ability of parent self-report harm avoidance scores to predict self-report of GAD diagnosis. This model was also found to be significantly different than the random predictor ($AUC = .500, P < .001$). A sensitivity of 90% was obtained between scores of 7 and 8, where the specificity was between 38% and 49%. As in the child data, this cut-off point is below the adult mean. A specificity of 90% was obtained at a cut-off of 15–16, where the sensitivity was between 48% and 56% (Fig. 3).

Fig. 4 demonstrates the distribution of HA scores obtained for all adult participants as well as the breakdown of the frequency of GAD diagnosis corresponding to each particular HA

score. Results were similar to those seen in children and adolescents. Of the 16 adults with HA scores more than 1.5 standard deviations above the mean, 9 (56%) had GAD. As can be seen from the figure, no subject with GAD had a HA score lower than 7. While this argues for some degree of specificity, GAD was frequently found in subjects with intermediate scores as in the child group.

4. Discussion

This study tested the degree of overlap between the temperamental dimension of harm avoidance and a corresponding psychiatric disorder, GAD, using receiver operating characteristic analysis. To our knowledge, it is the first attempt to apply this type of analysis to the link between temperament and psychopathology in a child sample. Consistent with our hypothesis, high levels of harm avoidance, an established trait referring to a tendency towards worry, shyness, and fatigability, showed a strong but certainly not complete association with the diagnosis of GAD. ROC analyses revealed highly significant AUC scores for both children (.791) and adults (.818). To offer some perspective for these AUC numbers, values are comparable to other diagnostic tests commonly employed in the medical community. The digital mammogram, used in diagnosing breast cancer has an AUC of .715 (Cole et al., 2004); the dexamethosone suppression test for predicting major depressive disorder has an AUC of .79 (Mossman & Somoza, 1989). An AUC of .67 was found in the prediction of clinical signs of pneumonia and confirmatory radiological diagnosis (Lynch, Platt, Gouin, Larson, & Patenaude, 2004).

No sex or age differences were found. The similarities between the child and adult AUC curves obtained here thus offer initial evidence that overlap between clinically significant levels of anxiety in individuals with a temperamental predisposition is similar in both children and adults.

Given the measurement error inherent in the assessment of both HA and GAD, even using a multiple informant approach, it would be unrealistic to require perfect overlap between HA and GAD even if GAD was simply the extreme end of a normal distribution of HA. How high, then, would the AUC need to be to infer a spectrum model given measurement limitations? While there is no universal cut-off, some previous work may be illustrative. For example, previous studies from this sample looking at the AUC between two measures of psychopathology such as the AUC between the quantitative attention problems score of the Child Behavior Checklist (which does not purport to measure ADHD per se) and the presence of DSM-IV ADHD were between .841 and .901 (Hudziak et al., 2004). Other studies measuring the AUC between a quantitative rating scale for a particular disorder and the presence or absence of its corresponding DSM diagnosis have been found to be .980 and above (Furlanetto, Mendlowicz, & Romildo Bueno, 2005; Mennin et al., 2002).

Thus, while strong overlap was found, high levels of harm avoidance do not appear to be necessary nor sufficient to determine the diagnostic status of children and adults. Also consistent with our hypothesis was that results indicated poorer sensitivity and somewhat better specificity in the prediction of GAD from HA scores. To summarize these findings qualitatively, high levels of HA were frequently not associated with GAD. In children, only half of those with HA scores 2 standard deviations above the mean or higher had a diagnosis of GAD. From the other perspective, GAD was over-represented in individuals with high HA but could often be seen in individuals with moderate levels of HA and was rarely seen in people with low HA. The results of the current study replicate previous research which has demonstrated strong but imperfect links between temperament and psychopathology and offer a quantitative evaluation of the degree of overlap.

While these discontinuities found between HA and GAD could reflect assessment errors despite our multiple assessment techniques, they may also represent a subgroup of individuals in which GAD symptomatology is more distinct from their personality. How could this occur? One possibility is that individuals with high HA and no GAD have more developed coping or emotion regulation skills that prevent temperamental predispositions from becoming clinically impairing. Similarly, individuals with poor emotional regulation skills could be impaired at more moderate levels of harm avoidance. Replication of these results using other instruments and other diagnoses will be critical to assess the generality of these findings.

Advances in our understanding of the continuities and discontinuities between temperament and psychopathology is highly valuable from both research and clinical perspectives, as levels of specific temperamental traits in children can often be observed well before the full onset of psychopathology. The factors that account for any discontinuities could provide important clues with regard to developmental psychopathology and prevention. These data also raise the important question of whether or not individuals with GAD and high harm avoidance are different from individuals with GAD and moderate harm avoidance in other meaningful ways such as illness phenomenology, underlying neurobiology, or treatment response. Research in other areas such as eating disorders has demonstrated that subtyping individuals based on personality may reveal more important differences than even their specific DSM disorder (Westen & Harnden-Fischer, 2001). Behavioral and molecular genetics studies could indicate, for example, the presence of different genes in the subpopulation of individuals with high HA and no anxiety disorders. Different patterns could also be investigated in neuroimaging studies. In summary, understanding personality profiles may provide an important advance in phenotypic refinement on which so much of clinical research depends.

Currently, however, the practical application of using temperamental tests to screen for anxiety disorders remains to be seen. Longitudinal studies have demonstrated many statistically significant associations between temperamental traits and later anxiety disorders; however, many, if not most, individuals would not be correctly classified (Kagan, 1994). Our own cross-sectional data documenting the difficulty of finding a cut-off point for harm avoidance scores that would result in satisfactory sensitivity and specificity does not support the use of this strategy, at least for this scale and without other corroborating information. Valid sensitivity and specificity information, however, can only be obtained when the cut-off scores generated from this sample are applied to others.

Limitations of the present study include similarities in the descriptions of harm avoidance and GAD. Although there is some item overlap between the TCI and the diagnostic criteria of GAD, associations between temperament and psychopathology have been found to be preserved even when overlapping items are removed (Lemery, Essex, & Smider, 2002). The extent of discontinuities in this study also argues against temperament and psychopathology simply being two different descriptions of the same entity. Furthermore, while the degree of item overlap invites criticism that the temperamental measure is simply picking up psychiatric symptoms, an equally valid argument could be made in the reverse direction. It is likely that there are state and trait components to both temperament and psychiatric disorders that mutually influence the other (Pelissolo & Corruble, 2002). Research has demonstrated, for example, both the partial “normalization” of harm avoidance in patients treated with medications for depression (Hellerstein, Kocsis, Chapman, Stewart, & Harrison, 2000) as well as the persistence of an anxious temperament before and after acute bouts of illness (Holtkamp, Muller, Heussen, Remschmidt, & Herpertz-Dahlmann, 2005). It has been hypothesized, based partially on these data, that some personality traits, such as harm avoidance, have more state-dependent qualities than others such as novelty seeking or

reward dependence (Öngür et al., 2005); however, this finding may also reflect the bias that most of this research has been carried out with antidepressants. Studies examining other psychopharmacological agents, in addition to longitudinal analyses that can look specifically at the developmental progression of traits and symptoms over time, are needed to untangle this complex association.

A second limitation concerns the homogeneity of our sample, which is comprised primarily of Caucasian-Americans individuals from middle-class backgrounds. As a result, we are unable to determine whether these findings could be replicated in ethnically diversified samples. Related to this point is that probands for this sample were recruited for the presence of attention problems and aggression. While we did not find differences between the probands and their siblings who were not screened for these problems, it is possible that different associations between harm avoidance and GAD would be found in a community sample or a sample recruited for internalizing disorders. It also remains to be seen whether similar relations will be found between other temperamental traits such as extraversion or activity levels and other psychiatric disorders such as attention-deficit/hyperactivity disorder.

In spite of these limitations, the quantifying of the continuities and discontinuities between temperament and anxiety diagnoses found in the present study may help shape future discussions concerning the degree to which temperamental traits are necessary or sufficient conditions for psychopathology. Further research including similar analyses of temperament and other psychopathologies as well as further study of the presence or absence of particular traits in certain disorders represents a meaningful advance in phenotype refinement and is clearly indicated. To date, these and other data suggest that enhanced understanding of temperament–psychopathology relations will have important implications for both assessment and clinical prevention of significant psychiatric symptoms.

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Fig. 1. Receiver operating characteristic curve for the prediction of current generalized anxiety disorder from harm avoidant score in children and adolescents ($AUC = .791$).

Fig. 2. Graph of distribution of harm avoidant scores and presence/absence of current DSM-IV generalized anxiety disorder in children and adolescents.

Fig. 3. Receiver operating characteristic curve for the prediction of current generalized disorder from harm avoidant score in adults (AUC = .818).

Fig. 4. Graph of distribution of harm avoidant scores and presence/absence of current DSM-IV generalized anxiety disorder in adults.

Table 1

Sample characteristics

	Child sample (<i>N</i> = 334)		Adult sample (<i>N</i> = 231)	
	Mean	S.D.	Mean	S.D.
Gender (male)	60%		27%	
Age (years)	10.44	2.87	40.46	5.96
SES	6.38	2.15	6.60	2.04
CBCL total problems (<i>T</i> score)	55.24	13.99	NA	
Other current diagnoses				
ADHD% (yes)	43		13	
ODD% (yes)	30		3	
CD% (yes)	13		2	
OCD% (yes)	1		0	
SAD% (yes)	7		3	
MDD% (yes)	7		11	
BDP% (yes)	7		11	

SES: socioeconomic status; CBCL: Child Behavior Checklist; ADHD: attention deficit hyperactivity disorder; ODD: oppositional defiant disorder; CD: conduct disorder; SUD: substance use disorder; GAD: generalized anxiety disorder; OCD: obsessive-compulsive disorder; SAD: separation anxiety disorder; MDD: major depressive disorder; BPD: bipolar disorder; Dysth: dysthymic disorder; NA: not applicable.

Table 2

Sensitivity and specificity of mean harm avoidant scores in predicting current diagnosis of GAD

Score	Child sample (<i>N</i> = 334)		Adult sample (<i>N</i> = 231)	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
0	100	0	100	0
1	98	1	100	6
2	98	4	100	11
3	98	11	100	15
4	98	19	100	20
5	98	28	100	27
6	95	36	100	33
7	88	45	93	38
8	83	56	89	49
9	80	63	85	54
10	73	71	85	57
11	63	77	78	64
12	61	82	74	70
13	54	87	67	78
14	37	92	67	83
15	32	97	56	88
16	19	98	48	93
17	12	98	33	96
18	12	99	22	98
19	10	99	4	100
20	2	99	0	100
21	0	100	0	100
22	0	100	0	100