University Utrecht
Master Neuropsychology

THESIS

The DAOA region is an effect modifier in predicting positive, negative and disorganized schizotypal symptoms in healthy participants

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The effect of the DAOA region on schizotypal symptoms has been very contradictory, and research of the effect of this region in healthy subjects is lacking. This pilot study measured variation on the DAOA SNP rs3918342; childhood trauma, recent life events, recent daily hassles, neuroticism, working memory and IQ; and positive, negative and disorganized schizotypal symptoms. 68 healthy participants from a suburb of Utrecht were tested, 34 with variant C/C and 34 with variant T/T. The groups did not differ in age, sex, schizotypal symptoms or any of the other variables. However, Gene x Environment interactions were found, with neuropsychological functioning being a more important predictor of schizotypal symptoms in the group with variant C/C and daily stress being more important in the group with variant T/T. Research results of the DAOA region have been contradictory, but this pilot study has shown that in healthy participants, instead of a direct effect on schizotypal symptoms, DAOA modifies the effect of environmental factors, particularly cognitive functioning and stress.

Introduction

Variations on a region of chromosome 13 have been associated with schizophrenia and bipolar disorder (Detera-Wadleigh & McMahon, 2006), panic disorder (Hamilton et al., 2003), unipolar depression (Rietschel et al., 2008) and autism (Chung, Hong, & Yoo, 2007). This mostly corresponds with a region that transcribes to D-amino acid oxidase activator (DAOA or G72), an enzym that possibly influences the effect of D-amino acid oxidase (DAO), which is an enzym that catalyses D-Serine, and D-serine influences the effectiveness of NMDA receptors (Boks et al., 2007).

DAOA is mostly associated with psychosis proneness (Shi, Badner, Gershon, & Liu, 2008), a very important current theme. However, there is much uncertainty about the effect of DAOA, and a many contradictions have been found (Detera-Wadleigh et al., 2006).

Genetic variation in the DAOA region concerns single-nucleotide polymorphisms (SNPs), a variation that occurs when a single nucleotide in the genome differs between humans, on both chromatids. A set of SNPs on a single chromatid that are statistically associated is called a haplotype. The variation on these SNPs (and thus, haplotypes) is thought to identify all other polymorphic sites in its region. The genetic structure of DAOA consists of several haplotypes, which vary somewhat independently of each other. Results found on one SNP are relevant for DAOA as a whole and thus, for every other haplotype block. One of the SNPs that has been associated in earlier scientific research

within Caucasian subjects is rs3918342, the marker for block M23. The variations are homozygote C/C, homozygote T/T or bizygote C/T. However, which one of these is the risk variant is unclear.

Associations of M23 variation with schizophrenia have been shown by many studies (Korostishevsky et al., 2004) In these studies homozygote T/T variation on M23 was shown to be more common in participants with schizophrenia. Homozygote T/T variation on M23 was also found to be a risk variant for Bipolar Disorder (Bass et al., 2009). Surprisingly, in other studies (i.e. Hattori et al., 2003; Schumacher et al., 2005) the homozygote C/C variation on M23 was the risk variant for schizophrenia. M23 is also significantly associated with neuroticism and depression (Rietschel et al., 2008), as well as panic disorder (Schumacher et al., 2004) and Bipolar Affective Disorder (Schumacher et al., 2005) and in these cases participants with homozygote C/C were more at risk. Other studies have shown no association at all of M23, or any of the other SNPs on DAOA, with bipolar disorder or schizophrenia (i.e. Mulle, Chowdari, Nimgaonkar, & Chakravarti, 2005). Some researchers do not even clearly state which variant was the risk variant in their study, while others (i.e. Detera-Wadleigh et al., 2006) emphasise the importance of these contradicting findings.

With respect to the relation with cognitive function, healthy subjects with the M23 homozygote C/C variant achieve higher test scores on tests of working memory and attention (Jansen et al., 2009). In both schizophrenia patients and healthy controls, carriers of the risk variant of the block 1 region on DAOA were significantly better at a semantic fluency task (Opgen-Rhein et al., 2008). In a population of patients with bipolar disorder another risk variant SNP (rs2391191) of DAOA is associated with reduced visuospatial properties (Soronen et al., 2008).

Research into the function of and associations with DAOA is growing, but much is still unknown. Especially the contradictory results regarding cognitive performance and which genotype is the actual risk variant are a reason to take a closer look at this region. Apparently this genomic region is highly versatile with a broad range of associations with diseases and psychological functioning. This makes it unlikely that there is a straightforward association between a certain marker within this region and a complex disease like schizophrenia. It is more likely that the association with DAOA variants

depends on the interplay between DAOA and other factors, both genetic and environmental, such as early life events. These so-called gene-environment (GxE) interactions gained much attention in recent years. For several other genes promising results have been reported (Murgatroyd et al., 2009; Thapar, Harold, Rice, Langley, & O'donovan, 2007).

GxE interactions are most likely to be found for pathologies with substantial environmentally mediated risks, but heterogeneity in vulnerability to these risks (Rutter, Moffitt, & Caspi, 2006). Schizophrenia fits this description. In addition, a genetic region is a candidate for GxE interactions if there is evidence of a substantial genetic effect, but also evidence that this is not a direct effect on pathology (Rutter et al., 2006). As described above, the DAOA region is strongly associated with schizophrenia, but a direct effect has not been found; rather, there are many contradictory findings. It might be that a more comprehensive analysis, taking interactions into account, of the association of DAOA variants can shed light on the influence of the DAOA region.

Of course the variables that seem to be influenced by DAOA, such as neuropsychological performance and psychopathology, are also associated with each other.

According to the DSM-IV-R (American Psychiatric Association, 2008), the essential features of schizophrenia are a mixture of positive, negative and disporganized symptoms. Examples are delusions or hallucinations (positive symptoms); affective flattening, avolition or alogia (negative symptoms); and disorganized speech such as frequent derailment or incoherence (disorganized symptoms). Although schizophrenia is diagnosed as a single disorder, there is much debate about the schizophrenia concept. Many studies in the past have emphasized the importance of differentiating between these symptom clusters. On the other hand, the latest recommendations for the DSM-V include removal of the paranoid, catatonic and disorganized subtypes of schizophrenia, thus focusing less on the difference between these symptom clusters. Regardless of the validity of the concept of schizophrenia as a whole, the different symptom clusters are reported to be associated with different vulnerability factors.

For example, many studies report childhood trauma as a risk factor for the development of schizophrenia or schizotypal personality disorder (e.g. Berenbaum, Thompson, Milanek, Boden, & Bredemeier, 2008). More childhood trauma has also been associated with a higher amount of sub-clinical schizotypal symptoms, particularly paranoia/suspiciousness and unusual perceptual experiences, but not magical thinking (Steel, Marzillier, Fearon, & Ruddle, 2009). This indicates that childhood trauma could be associated more with some schizotypal symptom clusters than with others.

A large number of life events is also associated with higher psychosis proneness. People who have experienced more life events in the past 6 months have a higher chance of acute psychosis (Bebbington et al., 1996). In addition, a high score on neuroticism is a suitable predictor for later psychotic symptoms (Krabbendam et al., 2002). The stress that patients experience (the amount of daily hassles) is also associated with symptoms of schizotypal personality disorder. A higher amount of daily hassles is a suitable predictor for more positive symptoms over time (Tessner, Mittal, & Walker, 2009). However, daily hassles are of course no independent variable. Life events and particularly neuroticism are indicators for the amount of stress a person experiences (Ormel & Wohlfarth, 1991). Perhaps the influence of life events and neuroticism on psychotic symptoms is not a direct influence, but is rather a matter of a higher vulnerability for experiencing stress, which then influences psychotic symptoms.

Performance on neuropsychological assessment has been associated with psychosis proneness as well. For example, a longitudinal study demonstrated that a premorbid lower IQ score was associated with increased risk of schizophrenia (Davidson et al., 1999; Zammit et al., 2004). High risk subjects also presented with a lower IQ score (Brewer et al., 2005) and a lower score on working memory and attention tests (Lencz et al., 2006). Working memory problems were also found in subjects with schizotypal personality disorder (Roitman et al., 1997). The importance of problems in working memory in schizophrenia is supported by studies that show abnormal functioning of the medial frontal cortex in patients with schizophrenia (Pomarol-Clotet et al., 2010). These studies show that neuropsychological deficit is present before the onset of psychosis, and we hypothesize that those subjects with higher psychosis proneness will demonstrate more neuropsychological deficit.

The factors that were described are associated with each other, and there seems to be a hierarchy. As Toates discusses, one can speak of lower level and higher order aspects of neuropsychology (Toates, 2006). At the lower level, there is not much consciousness; this is the basis of information processing. Examples are unconscious emotional processing, motor and sensory processes and procedural memory. Attention also belongs here; in as far as it modulates the sensory processes. Higher order processes include aiming for expectations and goals, higher order emotional processes (i.e. neuroticism) and declarative memory (semantic and episodic). This divide is particularly relevant for the current research, as, like Toates addresses: "Schizophrenia can be characterized in part by a chronic shift of weight from higher-order to stimulus based controls." (p. 106) In analogy of Toates, we hypothesise a number of hierarchies.

Working memory is a lower order process than intelligence, so working memory is expected to be a predictor for IQ, while IQ itself is then a predictor for the highly complex schizotypal symptoms. Previous studies have found working memory deficits to underlie declines in IQ (Schatz, Kramer, Ablin, & Matthay, 2000). Of course, working memory is strongly related to intelligence. In measuring intelligence, working memory is one of the aspects of a person's cognitive abilities that is being measured. Although intelligence is a concept that is used widely, there is still much debate on what intelligence is. One of the widely used definitions is from Wechsler (1974): 'Intelligence is the overall capacity of an individual to understand and cope with the world around him. This definition conceives of intelligence as an overall or global entity; that is, a multi-determined and multi-faced entity rather than an independent, uniquely-defined trait. It avoids singling out any ability, however esteemed (e.g. abstract reasoning), as crucial or overwhelmingly important.' Intelligence can thus be considered a general indicator of cognitive ability, whereas working memory, although one of the aspects of intelligence, is in itself a more basic aspect of cognitive ability. For example, Garlick and Sejnowski argue that working memory is an aspect of fluid intelligence, but that particularly abstraction, which is not measured with working memory tasks, is an important part of fluid intelligence (Garlick and Sejnowski, 2006).

Another hierarchy concerns the influence of M23/DAOA. It is possible that genetic vulnerability does not influence schizotypal symptoms directly. Rather, it is hypothesized to influence the amount of life events, stress experienced, neuroticism and neuropsychological functioning. These variables then, as discussed above, influence the vulnerability for schizotypal symptoms.

One last possible hierarchy is a different kind of influence of M23/DAOA. The pathways from lower order processes to higher order processes, could work differently in those with a genetic vulnerability. Genotype changes the way that the environment leads to psychopathology. The effects of life events, stress, neuroticism and neuropsychological functioning on schizotypal symptoms are modified by M23.

The review above shows that the interaction of these variables is complicated and as of yet unclear, which means that more research is necessary to understand the genetic building blocks of emotion, cognition and behaviour. It is possible that a better understanding of the interactions between these variables can help to clarify the influence of DAOA. So far, 1-on-1 interactions have not demonstrated a clear result. Almost all of the research on DAOA so far has focussed on patients with schizophrenia or bipolar disorder and the conclusion is that DAOA has contradicting effects in patients with extreme phenotypes. The few studies focussing on healthy participants and looking at the DAOA variants have found an effect on cognition (Jansen et al., 2009). This pilot study will look at healthy subjects and compare environmental factors, schizotypal symptoms and their interactions for the groups with different M23 variants.

Taking into account the different pathways towards schizotypal symptoms can help achieve clarity regarding the influence of DAOA on vulnerability for psychoses. It is expected that a Gene x Environment interaction will be found, rather than a direct effect. The goal of this pilot-study is to test knowledge about the pathways towards schizotypal symptoms and to understand the part that genetic vulnerability plays in this. This can result in increased clarity regarding the influence of life events and neuropsychological functioning on psychopathology and can be a valuable addition to several fields, one if which is the field of neuropsychology.

This study will examine the influence of variants of G72 (DAOA) in the healthy population. In particular, the importance of recent life events, recent daily hassles, childhood trauma, personality (*neuroticism*), neuropsychological functioning (*working memory and IQ*), and psychopathology (*psychosis proneness*) will be studied. Because this is a pilot study, meant to inspire future research, effect sizes of .24 or larger (medium and up) are considered important, regardless of significance.

Hypothesis 1: The number of positive, negative and disorganized schizotypal symptoms experienced will be different for participants with different M23 variants.

Hypothesis 2: The effect of M23 type is indirect, through life event, stress related and cognitive variables which then influence schizotypal symptoms. Therefore, the amount of childhood trauma, recent life events, recent daily hassles, neuroticism, working memory and IQ will be different for those in the M23 C/C group than in the M23 T/T group.

Hypothesis 3: There will be an effect of childhood trauma, recent life events, daily hassles, neuroticism, working memory and IQ on schizotypal symptoms. M23 acts as an effect modifier on this. In other words, the effect sizes of these variables on schizotypal symptoms will be different in the group with M23 variant C/C than in the group with M23 variant T/T.

Hypothesis 4.1: Schizotypal symptoms are not predicted by recent life events or neuroticism (only) directly, but these factors influence the amount of stress ('recent daily hassles') experienced, which then predicts schizotypal symptoms. These pathways work differently in the different M23 groups. The effect of neuroticism and daily hassles on schizotypal symptoms will be changed through the addition of these pathways.

Hypothesis 4.2: Working memory predicts IQ score and IQ score then predicts schizotypal symptoms. These pathways work differently in the different M23 groups.

Finally, because much is still uncertain about the influence of DAOA on schizotypal symptoms, it is possible that a different model would be a better predictor. Therefore an explorative data driven post-hoc analysis will be done, using structural equation modelling (SEM), to discover which combination of variables is the best predictor in the current dataset. If the model from the post-hoc analysis is in line with the hypothesis driven model this is circumstantial evidence supporting the initial hypothesis.

If other pathways come forward from the data-driven SEM, this could give direction to further research. A more comprehensive analysis of the full data set falls beyond the scope of this paper. Hopefully, a complete SEM will produce interesting effects to be looked into in the future.

Methods

1. Participants

All participants are healthy, independently living adults who have been a part of the Leidsche Rijn Gezondheids Project (LRGP) (Grobbee et al., 2005) seven to ten years ago. At that time all inhabitants of the Leidsche Rijn, a Dutch suburban area located in Utrecht, were asked to participate in the LRPG. Subjects who gave informed consent filled out questionnaires and had blood samples taken. For the current study, analyses were done to determine the genotype of participants who had agreed to be approached for further studies. Two groups were selected on the basis of DAOA SNP rs3918342 (M23) (homozygote C/C and homozygote G/G) and matched on age and gender. A quality control on genetic background was done to determine whether everyone was Caucasian, because the effect of DAOA can be different for other ethnicities. They were invited by letter, which detailed many aspects of the study, and then called. Everyone who agreed was either seen in the University Medical Center Utrecht (UMCU), or at the G.P. building in the Leidsche Rijn, for about 2.5 hours. They also received a password to log in on the website to fill out a variety of questionnaires, which took approximately 1.5 hours. The Medical Ethics committee of the UMCU approved both the LRPG and this study.

Participants who, at the time of writing, had not finished both the online questionnaires and the neuropsychological examination, were excluded from analysis. Both the T/T group and the C/C group consisted of 34 participants. All participants were between the ages of 25 and 65, and there was no significant or relevant age difference between the groups ($F = .780$; $p = .380$) (see table 1a). Neither was there a significant or relevant sex difference between the groups (Pearson's Chi square = .236, $p = .808$) (see table 1a).

2. Data

Four subtests of the Dutch Wechsler Adult Intelligence Scale (WAIS-III-NL; Wechsler, 2000; 'Coding', 'Block Design', 'Arithmetic' and 'Information') were administered. On a laptop, the N-Back (Callicott et al., 1998) was administered. Participants had to look at four red circles and determine which one was yellow now, the last time, two times ago, three times ago and four times ago. The total number of hits was determined. As Callicott and colleagues demonstrated, this test is related to frontal functioning in the brain and measures working memory. Online, participants filled in the NEO-PI-R (neuroticism subscale; Hoekstra, Ormel, & Fruyt, 2007), as well as the Recent Health Questionnaire to determine daily hassles in the past year and the Recent Life Events to determine significant life events such as death of a spouse in the past year, as used in the Utrecht Health Project (Grobbee et al., 2005). The Childhood Trauma Questionnaire (Bak et al., 2005) was also administered to determine the total amount of childhood trauma participants experienced. For a list of example questions from the questionnaires, see Addendum 2. The results from the NEO-PI-R neuroticism subscale were transformed into normed data, based on age and sex. Results from the four WAIS subtests were transformed into normed subscores, and then used to estimate a total IQ score. The childhood trauma questionnaire results were split into two groups based on the median: those with a low amount of childhood trauma (n=32) and those with a high amount of childhood trauma (n=36).

The most important dependent variable in this research is schizotypal personality. Schizotype is seen as a subclinical form of schizophrenia, with subclinical psychotic behaviour. It is probably caused by the same biological factors which cause schizophrenia (Roitman et al., 1997). Schizotype is present in the healthy population and signals psychosis proneness. The Schizotypal Personality Questionnaire (SPQ; Raine, 1991) has participants determine whether certain statements apply to them. These statements taken together form the nine criteria for Schizotypal Personality Disorder in the DSM-IV-R (American Psychiatric Association, 2008). For every criterium, a total score is determined. Factor analyses shows that a three factor model is the most meaningful (Raine et al., 1994). The nine subscales are divided over the following three factors: 'Positive', 'Negative' and 'Disorganized'. As explained earlier, these three aspects of

schizotype correspond to the three types of symptoms that can be present in schizophrenia.

Due to a website error, 27 out of 68 participants had not answered the question 'People sometimes find it hard to understand what I am saying'. This is part of the subscale 'Odd speech', part of the disorganized symptom cluster. Imputation based on the other 73 questions on the SPQ was used to derive the most likely answer ('yes' or 'no') for these participants.

In our dataset, the effect sizes of the associations between these schizotypal symptomclusters are moderate to large, but the variables are by no means identical (see table 1b). In order to increase the understanding of schizotypy, analyses will be done for the three separate symptom clusters. However, schizophrenia as a whole is also important, and therefore initial analyses will also be done for the total amount of schizotypal symptoms.

3. Data analysis

In order to test for a difference in schizotypal symptoms, ANOVAs are done in the statistical program SPSS (SPSS for Windows, 2008). M23 type is the independent variable and schizotypal symptoms the dependent. Although there is no significant difference in age and sex between the M23 variant groups, the ANOVAs are repeated as ANCOVAs, where age and sex are added as covariates to ensure they provide no confounding effects. Similar ANOVAs and ANCOVAs are done to determine if M23 type has an influence on childhood trauma, recent life events, recent daily hassles, neuroticism, working memory and IQ. Linear regression analysis is done to determine the influence of the above mentioned variables on schizotypal symptoms, in the total group, the group of participants with variant C/C and the group of participants with variant T/T.

In analogy of Aguilera et al. (Aguilera et al., 2009), the comparison of the effect of environmental factors on schizotypal symptoms are done by computing these effects separately for both M23 variant groups. By doing it this way, easy comparison to the results of the structural equation models is facilitated. Effect sizes will be compared by taking the difference between effect sizes, and dividing it by the largest effect size. Any

difference over 25% of the largest effect size will be considered a difference that is a trend.

In order to test the more complicated models, this study uses Structural Equation Modeling (SEM; Pathway Analysis), using the Mplus software (version 5.21). This software was specifically designed for the application of SEM. This is a statistical analysis for the estimation and testing of (causal) correlation, using statistical data and qualitatively causal hypotheses. In Pathway Analysis these (causal) correlations are tested using a linear equation system. By combining the several (multiple) regressions into one model, more information can be gained regarding the interactions of the variables. To test the models in Mplus, a decision was made regarding which evaluation of model fit indices would be used. The Maximum Likelihood method was rejected because it is dependent on sample size. Both a comparative (based on comparison with a baseline model) and an absolute measure of fit (based on discrepancy between model and data) were chosen to ensure certainty about the model's worth. The comparative measure of fit chosen is the Comparative Fit Index (CFI). This index is not sensitive to a small sample size and is consistent across different estimation methods. A model is good if CFI > .95 (Jackson, Gillaspy, & Purc-Stephenson, 2009). The absolute measure of fit chosen is the Root Mean Square Error of Approximation (RMSEA). This index is also insensitive to sample size. A model is good if RMSEA < .06 (Jackson et al., 2009).

Results

1. Direct effect of M23 type on schizotypal symptoms and predictive variables

ANOVAs were performed to determine the direct influence of M23 type on schizotypal symptoms. This was not significant for positive symptoms, negative symptoms, disorganized symptoms or total schizotypal symptoms (see table 1a).

To test the effect of M23 type on variables which predict schizotypal symptoms, ANOVAs were performed with M23 type as fixed factor and these predictive variables as dependent variables. The amount of childhood trauma, recent life events, recent daily hassles, neuroticism, working memory and IQ is not significantly different for those in M23 group C/C compared with T/T (see table 1a). There is a small effect of M23 on IQ, where those with the C/C variant have an IQ of, on average, 5 points higher. There is also

a small effect of M23 on both disorganized and total amount of schizotypal symptoms, where those with the C/C variant experience more symptoms. However, due to the small group sizes, this could be due to chance. In order to fully comprehend the data, these analyses were all repeated as ANCOVAs, with age and sex as covariates. This made no relevant difference to the results.

A power analysis was done to determine how large an effect size this study could have found. For a beta of .80, an alpha of .05 and an N of 68, the effect size is .117. This means that, even if not corrected for multiple testing, an effect size equal to or larger than .117 would have been found significant for this sample. This is considered a small effect size (.10 = small, .30 = moderate, .50 = large; Cohen, 1992).

2. The influence of M23 as an effect modifier

To test whether the influences of childhood trauma, recent life events, recent daily hassles, neuroticism, working memory and IQ are different in the different variants of M23, linear regression analyses were done with these variables as independent variables and positive, negative or disorganized schizotypal symptom clusters, or total amount of schizotypal symptoms as a dependent variable. These analyses were done for the complete group and for the two separate M23 variant groups (see table 2a-2d).

The effect size of the influence of these variables on schizotypal symptoms is at least small in the total group. The effect of childhood trauma is different in the participants with different M23 variants. In the group with T/T, the effect is larger on positive symptoms than in the group with C/C. The effect of recent life events is slightly larger in the group with variant C/C, but only on disorganized symptoms. The effects of both recent daily hassles and neuroticism on positive and disorganized symptoms are larger in the group with variant T/T, but their effects on negative symptoms are larger in the group with variant C/C. The effect of working memory on all schizotypal symptoms is larger in the group with variant C/C. The effect of IQ is also larger in the group with variant C/C, on negative and disorganized symptoms.

3.1. The influence of a model with recent life events, stress and neuroticism, considering M23 as an effect modifier

To test whether recent life events and neuroticism influence stress, which then influences schizotypal symptoms, SEMs were done using the model in figure 1.

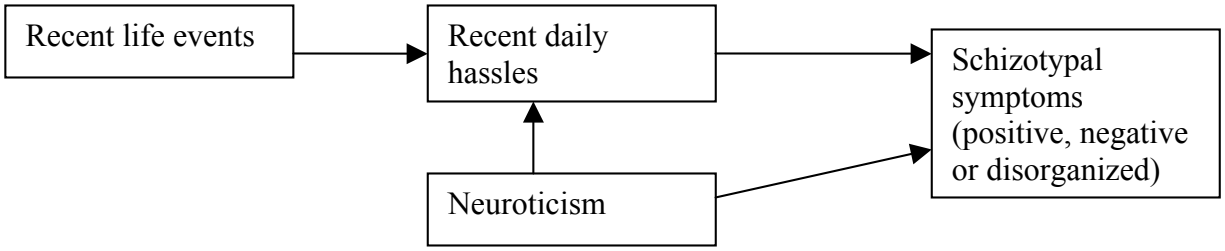

Figure 1. **The proposed model of the influence of recent life events, stress and neuroticism on schizotypal symptoms.**

These analyses were done for separate M23 variant groups. For all models, CFI: 1.000, and RMSEA: 0.000. This indicates a good model fit. The effect sizes of the influence of neuroticism on recent daily hassles ranges from .304 to .390, indicating that this is a moderate predictor of recent daily hassles. A higher neuroticism score indicates more stress experienced. The effect sizes of the influence of recent life events on recent daily hassles ranges from .312 to .343, indicating that this is a moderate predictor of recent daily hassles. A higher amount of recent life events indicates more stress experienced.

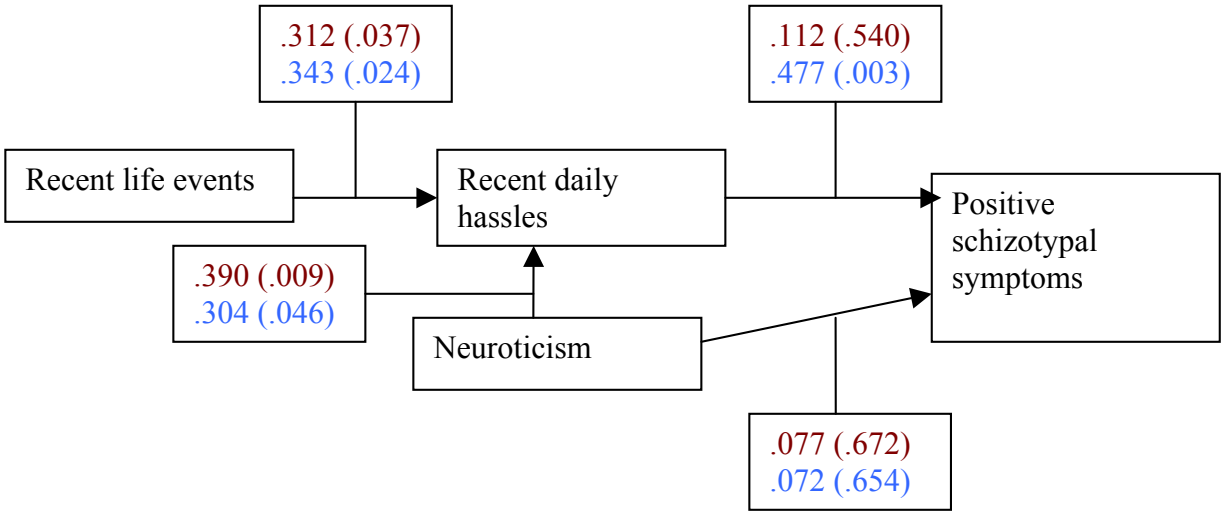

Figure 2. **The effect size of recent daily hassles and neuroticism as predictors of positive schizotypal symptoms, where red indicates the participants with the C/C variant and blue the participants with the T/T variant. Numbers are standardized regression coefficient first, then significance level.**

The effect size of neuroticism as a predictor of positive schizotypal symptoms is trivial for both groups. The effect size of recent daily hassles on positive schizotypal symptoms is small for participants with the C/C variant, and moderate for participants with the T/T variant. More stress experienced indicates more positive schizotypal symptoms. (see figure 2)

The difference between the C/C group and the T/T group for recent daily hassles predicting positive symptoms is 77%. The difference between the C/C group and the T/T group for neuroticism predicting positive symptoms is 6%.

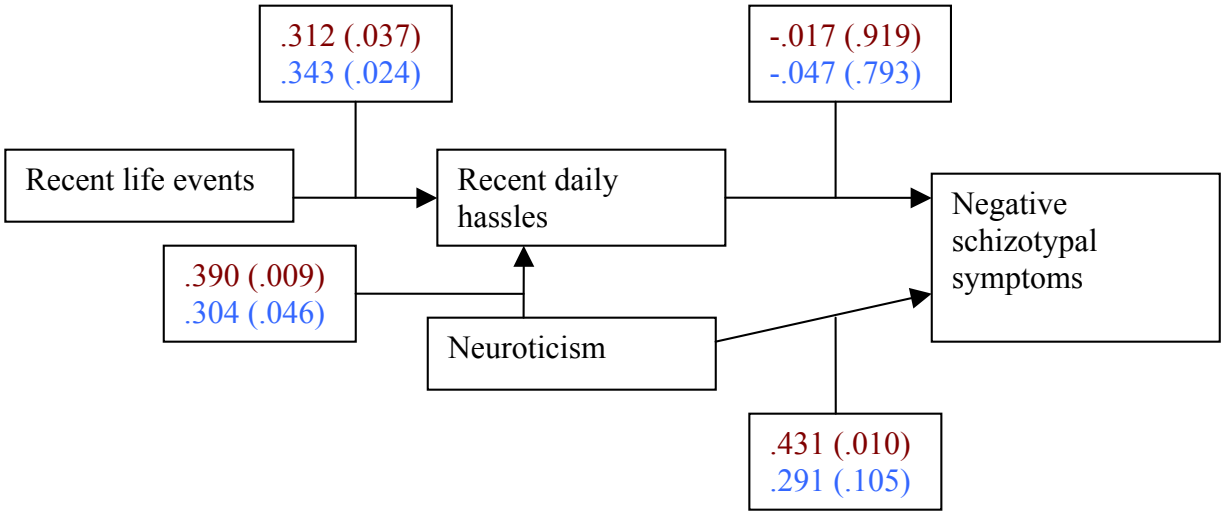

Figure 3. **The effect size of recent daily hassles and neuroticism as predictors of negative schizotypal symptoms, where red indicates the participants with the C/C variant and blue the participants with the T/T variant. Numbers are standardized regression coefficient first, then significance level.**

The effect size of neuroticism as a predictor of negative schizotypal symptoms is moderate for the participants with the C/C variant and small for the participants with the T/T variant. A higher neuroticism score indicates more negative schizotypal symptoms. The effect size of recent daily hassles on negative schizotypal symptoms is trivial for both groups. (see figure 3)

The difference between the C/C group and the T/T group for recent daily hassles predicting negative symptoms is 64%. The difference between the C/C group and the T/T group for neuroticism predicting negative symptoms is 32%.

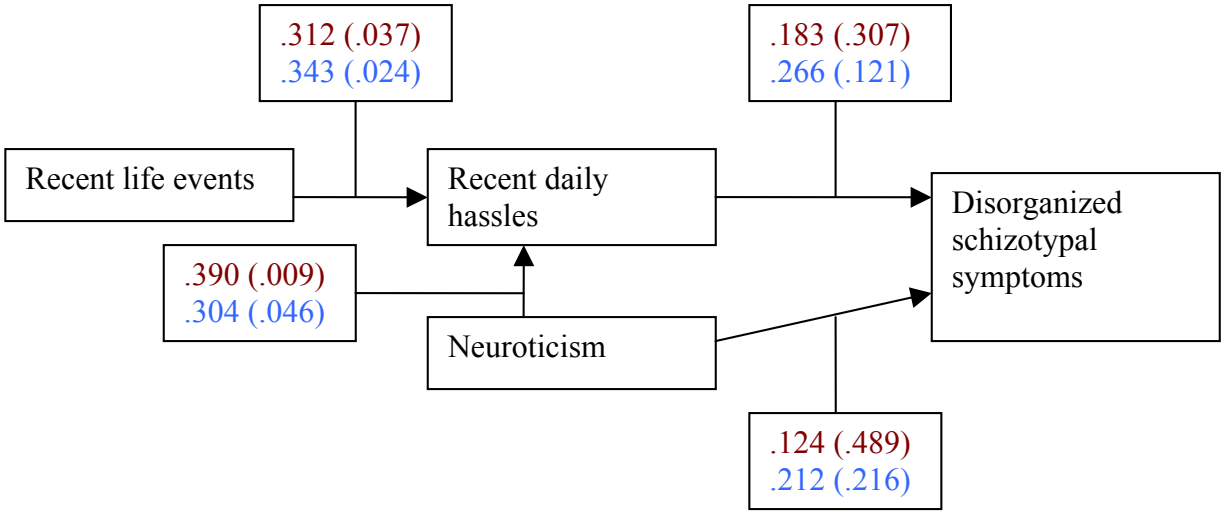

Figure 4. **The effect size of recent daily hassles and neuroticism as predictors of disorganized schizotypal symptoms, where red indicates the participants with the C/C variant and blue the participants with the T/T variant. Numbers are standardized regression coefficient first, then significance level.**

The effect size of neuroticism as a predictor of disorganized schizotypal symptoms is small for both groups. A higher neuroticism score indicates more disorganized schizotypal symptoms. The effect size of recent daily hassles on disorganized schizotypal symptoms is small for both groups. More stress experienced indicates more disorganized schizotypal symptoms. (see figure 4)

The difference between the C/C group and the T/T group for recent daily hassles predicting disorganized symptoms is 31%. The difference between the C/C group and the T/T group for neuroticism predicting disorganized symptoms is 42%.

Table 3. *The amount of variance in positive, negative and disorganized schizotypal symptoms explained (R^2) by the model of recent life events, recent daily hassles and neuroticism, for participants with the C/C variant and participants with the T/T variant.*

	Participants with C/C variant	Participants with T/T variant
Positive symptoms	.025	.260
Negative symptoms	.191	.076
Disorganized symptoms	.066	.160

As is shown in Table 3, in the participants with variant C/C, daily hassles and neuroticism can be used to explain 19% of variance in negative symptoms, but they do not explain much variance in positive or disorganized symptoms. In participants with

variant T/T, daily hassles and neuroticism can be used to explain 26% of variance in positive symptoms and 16% in disorganized symptoms, but they do not explain much variance in negative symptoms.

3.2. The influence of neuropsychological functioning, considering M23 as an effect modifier

To test whether working memory influences IQ, which then influences schizotypal symptoms, SEMs were done using the model in figure 5.

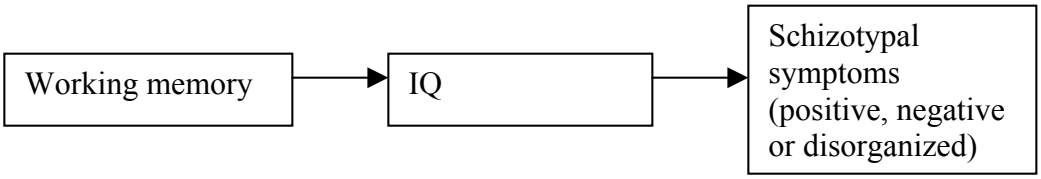

Figure 5. **The proposed model of the influence of working memory and IQ on schizotypal symptoms.**

These analyses were done for the two separate M23 variant groups. The effect sizes of the influence of working memory on IQ ranges from .452 to .550, indicating that this is a moderate to large predictor of IQ.

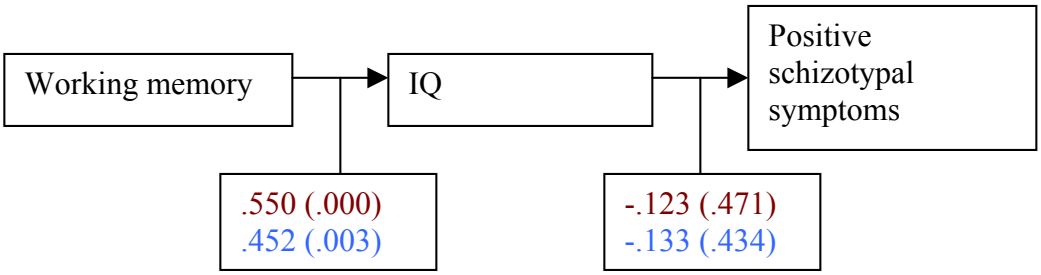

Figure 6. **The effect size of IQ as a predictor of positive schizotypal symptoms, where red indicates the participants with the C/C variant and blue the participants with the T/T variant. Numbers are standardized regression coefficient first, then significance level. C/C group: CFI: .984, RMSEA: .072. T/T group: CFI: 1.000, RMSEA: 0.000.**

The effect size of IQ on positive schizotypal symptoms is small for both groups. A higher IQ indicates fewer positive schizotypal symptoms. This model is a good fit for the group with the T/T variant and close to a good fit for the group with the C/C variant (see figure 6).

The difference between the C/C group and the T/T group for IQ predicting positive symptoms is 8%.

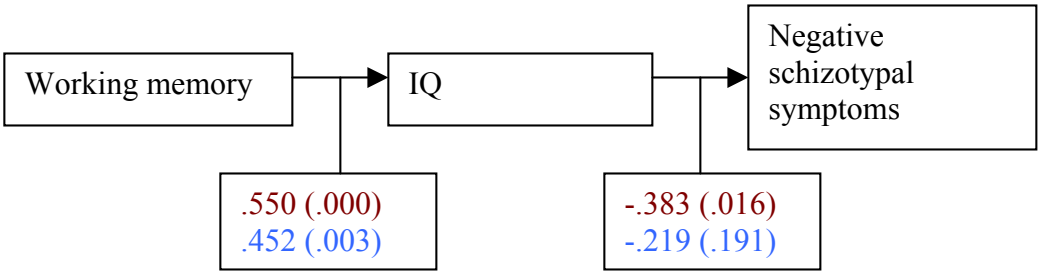

Figure 7. **The effect size of IQ as a predictor of negative schizotypal symptoms, where red indicates the participants with the C/C variant and blue the participants with the T/T variant. Numbers are standardized regression coefficient first, then significance level. C/C group: CFI: .916, RMSEA: .206. T/T group: CFI: .939, RMSEA: .119.**

The effect size of IQ on negative schizotypal symptoms is moderate for participants with the C/C variant and small for participants with the T/T variant. A higher IQ indicates fewer negative schizotypal symptoms. This model is not a good fit for either group (see figure 7).

The difference between the C/C group and the T/T group for IQ predicting negative symptoms is 43%.

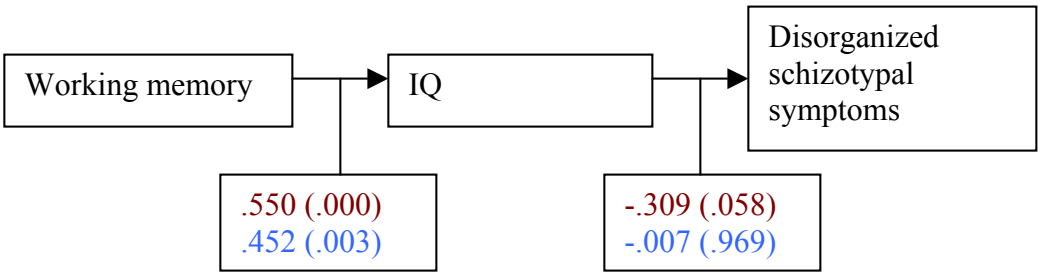

Figure 8. **The effect size of IQ as a predictor of disorganized schizotypal symptoms, where red indicates the participants with the C/C variant and blue the participants with the T/T variant. Numbers are standardized regression coefficient first, then significance level. C/C group: CFI: .743, RMSEA: .373. T/T group: CFI: 1.000, RMSEA: 0.000.**

The effect size of IQ on disorganized schizotypal symptoms is moderate for participants with the C/C variant and there is no effect for participants with the T/T variant. A higher IQ indicates fewer disorganized schizotypal symptoms. This model is a good fit for the group with the T/T variant and not a good fit for the group with the C/C variant (see figure 8).

The difference between the C/C group and the T/T group for IQ predicting disorganized symptoms is 98%.

Table 4. *The amount of variance in positive, negative and disorganized schizotypal symptoms explained (R^2) by the model of working memory and IQ, for participants with the C/C variant and participants with the T/T variant.*

	Participants with C/C variant	Participants with T/T variant
Positive symptoms	.015	.018
Negative symptoms	.147	.048
Disorganized symptoms	.095	.000

As is shown in Table 4, in the participants with variant C/C, working memory and IQ can be used to explain 14,7% of variance in negative symptoms, but they do not explain much variance in positive or disorganized symptoms. In participants with variant T/T, working memory and IQ do not explain much variance in any of the symptom clusters.

4. Total SEM -> data driven

An explorative data driven post-hoc analysis, using structural equation modelling, was done to find the best fitted model to this dataset. The command MODINDICES was used to determine which interactions were large enough to enter in the model. The direction of these interactions was based on the literature. A model that fitted well for each separate cluster of symptoms was created, and the results are given in the addendum (see figure 9-17). In order to optimize understanding, only those variables and arrows are added that pertain to schizotypal symptoms, either directly or indirectly.

Discussion

The aim of this pilot study was twofold: first, to understand the influence that DAOA genotype has on schizotypal symptoms in healthy participants. Second, because the influence that other variables have on schizotypal symptoms is still unclear, to look into the specific pathways towards schizotypal symptoms. The most important results were that the genetic variation of the DAOA region does not influence schizotypal symptoms directly, but interacts with the environment. The influence that childhood

trauma, recent life events, daily stress/hassles, neuroticism, working memory and IQ have on schizotypal symptoms depends on the variation of the DAOA region (see figure 18-20) Specifically, in the group with M23 variant C/C, cognitive functioning is an important predictor of schizotypal symptoms, whereas it has only a small effect in the group with variant T/T. On the other hand, recent daily hassles is an important predictor of schizotypal symptoms in the group with variant T/T, but not in the group with variant C/C.

This study has not found a direct effect of M23 variant on schizotypal symptoms or other variables. A small effect was found for M23 type on disorganized symptoms and on IQ, where those with variant C/C experience more disorganized symptoms and display a higher IQ. However, whether this is chance or a true (albeit small) difference is unclear. As expected, in the complete group many of these variables are predictors of schizotypal symptoms and have at least a small effect size on total amount of schizotypal symptoms (see table 2d). Recent life events and working memory have a trivial to small effect size on schizotypal symptoms. Childhood trauma, recent daily hassles, neuroticism, and IQ have a small to moderate effect size.

Schizophrenia is a heterogenous disorder. Many different symptoms combine to a diagnosis of schizophrenia, but there is not one symptom that is present in all patients. Generally, the symptoms are divided into three clusters: positive, negative and disorganized symptoms. Positive symptoms include hallucinations and delusions. Negative symptoms include affective flattening, avolition and alogia. Disorganized symptoms include frequent derailment or incoherence in speech (American Psychiatric Association, 2008). The underlying causes of these symptom clusters are unlikely to be identical. This study invested in looking at each cluster of symptoms separately and found the following predictors of positive schizotypal symptoms: childhood trauma, recent daily hassles and (in the group with M23 variant T/T) neuroticism (see figure 18). Negative schizotypal symptoms are predicted by childhood trauma, neuroticism, IQ and (in the group with M23 variant C/C) working memory (see figure 19). Disorganized symptoms are predicted by recent daily hassles, neuroticism and (in the group with M23 variant C/C) working memory and IQ (see figure 20).

The model of recent life events and neuroticism predicting daily hassles, and daily hassles and neuroticism predicting schizotypal symptoms (see figure 1) proved to be a well fitted model for both groups and all three schizotypal symptom clusters. Neuroticism and recent life events were both moderate predictors of daily hassles. Compared to simple linear regressions, the small predictive value of neuroticism on positive symptoms in both groups was lost when also taking stress into account.

The model of working memory predicting IQ and IQ predicting schizotypal symptoms (see figure 5), was a reasonable model in the group with variant T/T. However, in the group with variant C/C, the model was not a good fit. The influence of IQ on schizotypal symptoms was the same as in the simple linear regression.

When looking at the exploratory, data driven structural equation models, several things are important: in the group with variant C/C, the variables used in this study can explain between 19 and 30 percent of variation schizotypal symptoms. However, in the group with variant T/T, these variables explain less variation in negative and disorganized symptoms (21 and 16 percent, respectively), but over half of the variation in positive symptoms (53%). Therefore, in this study, the variables that were used were particularly useful in predicting the amount of positive schizotypal symptoms in participants with M23 variant T/T. The model concerning cognitive functioning did not surface in the group with variant C/C. Rather, working memory (instead of IQ) was found as a predictor of schizotypal symptoms. In the group with variant T/T, cognitive funtioning was only found as a predictor for negative symptoms, but in that case IQ was found as the primary predictor, which itself was predicted by working memory.

DAOA has been associated with schizophrenia, but the specific effect is unclear. Some studies report the T/T variant as the risk variant, but other studies report the C/C variant of the risk variant (Detera-Wadleigh et al., 2006). In this study, we did not look at patients with full blown schizophrenia, but rather at a healthy population. This way, we hoped to see if DAOA is only associated with full blown schizophrenia, or if it is also associated with sub-clinical schizotypal symptoms. And if it does, what M23 type variant is associated with more schizotypal symptoms. We used extreme genotypes (homozygote C/C versus homozygote T/T) to ensure the largest chance of finding results.

The M23 variants were not associated with schizotypal symptoms, nor with the other variables (see table 1a). With the group size of 68, any effect size over .117 should have been found (with power at .80). Therefore, we can say that M23 does not appear to have a medium or large effect size, on schizotypal symptoms or the environmental factors we measured. This is not surprising, because if there was such a large effect size, there would not be this much uncertainty regarding the effect.

M23 has neither a direct nor indirect effect on schizotypal symptoms. However, many studies have found contrasting effects of M23 when comparing patients with schizophrenia with healthy controls. Therefore, we expect that M23 could be an effect modifier. The way that life events, neuroticism and cognitive functioning influence schizotypal symptoms depends on the variant of M23, due to a Genotype x Environment interaction (Rutter et al., 2006). Confirming our hypotheses, different effects of environmental factors on schizotypal symptoms have been found in the genetically different groups. One of the strongest differences concerns daily hassles, which is a strong predictor of positive and negative schizotypal symptoms in the group with variant T/T, but not in the group with variant C/C (see table 2a and 2b). The influence of cognitive functioning is also different: both working memory and intelligence are predictors of negative and disorganized symptoms in the group with variant C/C. In the group with variant T/T, working memory has no effect and IQ only has a small effect on negative symptoms (see table 2b and 2c). It seems that in the group with variant T/T, stress and life events are the most important in predicting schizotypal symptoms. On the other hand, cognitive functioning is most important in the group with variant C/C.

As described above, different predictors were found for the three different clusters of schizotypal symptoms: positive, negative and disorganized symptoms. Recent daily hassles, or everyday stress, was associated with positive and disorganized symptoms, but not with negative symptoms. This has previously been found in a study of adolescents with schizotypal personality disorder, where more daily stressors predicted an increase in positive schizotypal symptoms, but not in negative schizotypal symptoms (Tessner, Mittal, Walker, 2009).

Neuroticism was associated with all aspects of schizotypal symptoms. This is consistent with previous literature, which shows that patients with schizophrenia show elevated levels of neuroticism, and those with higher neuroticism have a higher chance of developing schizophrenia, and in healthy subjects higher neuroticism is associated with all aspects of schizotypy (Horan, Blanchard, Clark, & Green, 2008).

Childhood trauma was associated with positive and negative symptoms, but not with disorganized symptoms. Previous studies have found an effect of childhood trauma on schizotypal symptoms in both healthy and patient populations (Berry, Band, Corcoran, Barrowclough, & Wearden, 2007; Ucok & Bikmaz, 2007). Berry et al. also found that the strongest effect of childhood trauma was on positive schizotypal symptoms.

Neuropsychological functioning was associated with negative and disorganized schizotypal symptoms, but not with positive schizotypal symptoms. This same result has previously been found in patients with schizophrenia (Basso, Nasrallah, Olson, & Bornstein, 1998; Brekke, Raine, & Thomson, 1995). Basso et al. found that negative and disorganized symptomatology was associated with poor intellectual functioning (as well as poor memory, attentional capacity, psychomotor speed and sensory-perceptual function). Spatial working memory has also previously been associated with disorganized symptoms and disfunction of the dorsolateral prefrontal cortex (Takahashi et al., 2005).

This discussion demonstrates that positive, negative and disorganized schizotypal symptoms share some vulnerability, but also show different vulnerabilities, which is in accordance with expectations.

A specific goal of this study was to gain more insight into the pathways that lead to schizotypal symptoms. The first pathway consists of recent life events and neuroticism combining to form daily hassles, or the amount of stress experienced (Tessner et al., 2009), and daily hassles and neuroticism then both predicting schizotypal symptoms (see figure 1). For every symptom cluster and for every genetic group, this model proved to be a good fit for the data. Recent life events and neuroticism were significant predictors of daily hassles. This provides an interesting idea: what is important is not the objective amount of life events that are experienced, but the subjective stressful value that is attached to them, as influenced by neuroticism. This pathway predicted up to 26% of the

variance of positive schizotypal symptoms, in the T/T variant groep. When looking at best fitted models for the data, this model also emerges: objective life events do not influence schizotypal symptoms directly, but their influence is dependent on the amount of stress that people actually experience, based on life events, neuroticism and possibly gender (with women experiencing more stress).

The second pathway consists of working memory predicting IQ (Toates, 2006; Schatz et al., 2000), and IQ then predicting schizotypal symptoms. This model proved to be a reasonable fit for the group with M23 variant T/T, but not the group with variant C/C. This indicates that this model is not perfect and a different model involving working memory and IQ could be a better predictor of schizotypal symptoms. As expected, working memory was a moderate to large predictor of IQ, and it explained up to 30% of the variance in IQ. This corresponds to the notion that working memory is one of the several aspects of cognition that result in intelligence, a general indicator of cognitive functioning. The predictive value of IQ is only significant for negative symptoms, in the total group and in the C/C variant group. It explains nearly 15% of the variance in negative symptoms. Much is still unclear regarding the specific influence that working memory and intelligence on schizotypal symptoms. This pilot study shows that perhaps it is not general cognitive ability (intelligence) that is most important in understand schizotypal symptoms, but that it is working memory in particular, one aspect of intelligence, that influences and is influenced by these symptoms.

When looking at best fitted pathway models based on the data, some interesting interactions appear. Childhood trauma influences schizotypal symptoms directly, but more childhood trauma is also associated with a higher neuroticism level. This result has previously been found in studies specifically targeting childhood trauma and personality (Allen & Lauterbach, 2007). It seems likely that experiencing trauma during childhood influences ones personality to become more neurotic. However, the fact that childhood trauma was reported years later on a questionnaire must also be kept in mind: it is possible that those with a more neurotic personality reflect back on the childhood as more traumatic, even if objectively they may not have experienced more trauma.

Another interesting correlation that emerges is that between IQ and neuroticism. Higher neuroticism has been associated before with lower scores on intelligence tests

(Ackerman & Heggestad, 1997; Moutafi, Furnham, & Paltiel, 2004). One possible explanation that has been put forward is that those with a higher level of neuroticism worry more during the intelligence test and are thus more distracted, thereby lowering their score. However, other explanations could be thought of, for example that those with a lower intelligence have more trouble finding a secure job and living situation, and are thus subject to more things to worry about.

The DAOA region has been associated with schizophrenia, but the findings have been contradictory (Detera-Wadleigh et al., 2006). There are several factors that influence this complexity. First of all, the DAOA region itself comprises several SNPs, which vary somewhat independently. Variation on many of these SNPs has been associated with schizophrenia, indicating that several nucleotides are important in understanding the effect of DAOA. Therefore, one cannot speak of two variants of DAOA, but rather there are many possible variants. In addition, schizophrenia as a psychopathology is still not very well understood. There is much debate about the validity of the 'schizophrenia concept'. This increases the complexity of understanding the influence of DAOA on schizophrenia, as there are in all likelihood different influences for the different symptom clusters.

However, by using a large amount of data about every participant, and by looking at it methodologically, it has become clear that the M23 point on DAOA is a strong candidate for Gene x Environment interaction. In the group with M23 variant C/C, neuropsychological functioning (both working memory and IQ) is associated with schizotypal symptoms. This association is not present in the group with M23 variant T/T. On the other hand, recent daily hassles is a strong predictor in the group with variant T/T, but unimportant in the group with variant C/C. As has been discussed, GxE interactions have gained much attention in recent years (Rutter et al., 2006) and this study shows that DAOA, or at least the M23 block, does not have a direct effect on psychopathology, but is another region that interacts with the environment in causing schizotypal symptoms.

Of course, several points of criticism can be constructed regarding this pilot study. First of all, the group existed of 68 people, and each subgroup of 34. In order to construct

more complex structural equation models, larger groups of people are needed. Generally, 5 – 15 people are advised for every parameter to be estimated. This means that for the model regarding life events (which has four parameters) and the exploratory data driven SEM, the subgroups for M23 variant type could be considered too small.

The population that has been chosen for this study is inhabitants of the Leidsche Rijn, a newly developed Dutch suburban area located near Utrecht. About 50% of those who were approached agreed to participate in this study. There might be a selection bias, whereby those with more problems and busier lives, such as single parents and or those with more than fulltime jobs, are not participating in this study. In addition, only people with four Caucasian grandparents were invited, because DAOA (and other genes) may have different effects in different ethnic groups. Therefore, all conclusions from this paper are only applicable to the Caucasian population.

Although many variables were measured in this study, and all were combined to create a best fitted model for the data, these variables could still explain only part of the variation in schizotypal symptoms. This indicates that some important predictors of schizotypal symptoms must be missing, which this study failed to measure.

Of course, there are also several strong points in this study. It measures healthy participants, something that is still relatively untouched in the field of DAOA. The amount of data available on every participants is large, giving us information about genotype, life events, personality, neuropsychological functioning and schizotypal symptoms. By combining all this information more becomes clear than if only a few of these variables had been measured. In other words, the dataset is quantitatively strong. The people performing the tests in this study were all academic Bachelors or Masters in psychology, and trained extensively, in order to ensure a qualitatively strong data set. This has resulted in a dataset with very few missing values, an important strength of this study.

We recommend that the results that were found in this study are replicated in a separate sample. The DAOA gene and environment interact to cause symptoms, and this should be looked into using a larger dataset. Particularly the influence of daily hassles and cognitive functioning on schizotypal symptoms have been found to be different for

the different DAOA variant groups. Future research should look into these variables more deeply. Furthermore, the effect of all these variables on psychopathologies other than schizophrenia should be studied, for example anxiety or mood disorders. Future research should also look into the possibility that pathways towards schizotypal symptoms and other psychopathologies are different for those with other genetic vulnerabilities than the M23 SNP on DAOA. The addition of pathway analysis, rather than simple linear regressions, can be a great help for this.

Cognitive functioning, particularly working memory, in patients with schizophrenia has been associated with abnormal frontal functioning in the brain (Henseler, Falkai, & Gruber, 2009). The fact that the model regarding neuropsychological functioning was not found to be a good fit in most groups, indicates that perhaps neurological functioning is also different in the separate genetic groups. Future research should attempt to understand brain functioning or structure differences between genetic groups. Another possible way that genes and environment interact is through environmentally induced epigenetic effect (Rutter et al., 2006). As knowledge about DNA increased, it emerged that the expression, or transcription, of genes can be changed by environmental factors. Future research should look into the expression of the DAOA region as a function of environmental factors.

Even though the variables used in this study were found to be predictors of schizotypal symptoms, a large part of the schizotypal symptom variance is still left unexplained. Future research should attempt to find the factors that explain this variance. Perhaps other aspects of personality besides neuroticism can be a valuable addition, or other measures of cognitive functioning. Of course, it is also possible that completely different variables are meaningful, for example religion or substance use.

One aspect of this study that is recommended for all future studies into schizophrenia, is the importance of trying to understand the separate symptom clusters. Schizophrenia is a varied disorder consisting of positive, negative and disorganized symptoms. As this study has shown, vulnerability factors for these different symptom clusters are not the same. Therefore, future research should attempt to understand the varied pathways that exist, and not try to explain the whole of schizophrenia with one single model.

Research results of the DAOA region have been contradictory, but this pilot study has shown that in healthy participants, instead of a direct effect on schizotypal symptoms, DAOA modifies the effect of environmental factors, particularly cognitive functioning and stress.

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ADDENDUM 1: tables 1-2, figures 9-20

Table 1a. *Descriptive statistics of the participants (average first, then std. dev.) for the complete group, the participants with C/C and the participants with T/T – as well as the results of an ANOVA comparing the two variant groups on these variables*

	Total group	C/C variant group	T/T variant group	ANOVA results
Sex	32 male, 36 female	15 male, 19 female	17 male, 17 female	F(1,66) = .230 p = .633 R^2 = .003
Age	43.84 (8.78)	42.9 (8.07)	44.76 (9.48)	F(1,66) = .754 p = .388 R^2 = .011
Childhood trauma	.529 (.5029)	.529 (.5067)	.529 (.5067)	F(1,66) = .000 p = 1.000 R^2 = .000
Recent life events	16.06 (1.16)	16.18 (1.14)	15.94 (1.18)	F(1,66) = .699 p = .406 R^2 = .010
Recent daily hassles	14.53 (2.32)	14.68 (2.25)	14.38 (2.41)	F(1,66) = .270 p = .605 R^2 = .004
Neuroticism	6.19 (2.02)	6.12 (2.16)	6.26 (1.90)	F(1,66) = .089 p = .766 R^2 = .001
Working memory	67.88 (11.60)	67.18 (11.45)	68.59 (11.88)	F(1,66) = .249 p = .619 R^2 = .004
IQ	108.78 (17.42)	111.53 (20.36)	106.03 (13.62)	F(1,66) = 1.713 p = .195 R^2 = .025
Positive schizotypal symptoms	.1369 (.1325)	.1496 (.1393)	.1243 (.1262)	F(1,66) = .616 p = .435 R^2 = .009
Negative schizotypal symptoms	.1868 (.1483)	.1939 (.1593)	.1797 (.1385)	F(1,66) = .154 p = .696 R^2 = .002
Disorganized schizotypal symptoms	.1385 (.1549)	.1604 (.15484)	.1167 (.1542)	F(1,66) = 1.357 p = .248 R^2 = .020
Total schizotypal symptoms	.1541 (.1122)	.1680 (.1212)	.1402 (.1022)	F(1,66) = 1.038 p = .312 R^2 = .015

Table 1b. *Pearson correlations of positive, negative and disorganized schizotypal symptoms*

	Positive schizotypal	Negative schizotypal

	symptoms	symptoms
Negative schizotypal symptoms	.384 p = .001	1
Disorganized schizotypal symptoms	.285 p = .018	.497 p = .000

Table 2a. *The results of regression analyses done to determine the influence of variables on positive schizotypal symptoms. Bold and red indicates an effect size of .30 or larger (medium and up; (Cohen, 1992)). Comparisons of the effect size (difference divided by largest effect size) are also given. Bold indicates a difference of more than 25%, red indicates the effect sizes are classified differently.*

	Total group	C/C variant group	T/T variant group	Comparison of effect size of C/C variant and T/T variant
Childhood trauma	**t(67) = 3.548** **p = .001** **β = .400** **R^2 = .160**	t(33) = 1.683 p = .102 β = .285 R^2 = .081	**t(33) = 3.557** **p = .001** **β = .532** **R^2 = .283**	**46%** **small vs.** **large**
Recent life events	t(67) = 1.090 p = .280 β = .133 R^2 = .018	t(33) = .690 p = .495 β = .121 R^2 = .015	t(33) = .733 p = .469 β = .128 R^2 = .017	5%
Recent daily hassles	**t(67) = 2.779** **p = .007** **β = .324** **R^2 = .105**	t(33) = .806 p = .426 β = .141 R^2 = .020	**t(33) = 3.318** **p = .002** **β = .506** **R^2 = .256**	**72%** **small vs.** **large**
Neuroticism	t(67) = 1.466 p = .147 β = .178 R^2 = .032	t(33) = .681 p = .501 β = .119 R^2 = .014	t(33) = 1.528 p = .136 β = .261 R^2 = .068	**54%** **small**
Working memory	t(67) = -.669 p = .506 β = -.082 R^2 = .007	t(33) = -1.278 p = .210 β = -.220 R^2 = .049	t(33) = .431 p = .670 β = .076 R^2 = .006	**135%** **small vs.** **trivial**
IQ	t(67) = -.881 p = .382 β = -.108 R^2 = .012	t(33) = -.699 p = .489 β = -.123 R^2 = .015	t(33) = -.759 p = .454 β = -.133 R^2 = .018	8%

Table 2b. *The results of regression analyses done to determine the influence of variables on negative schizotypal symptoms. Bold and red indicates an effect size of .30 or larger (medium and up;(Cohen, 1992)). Comparisons of the effect size (difference divided by largest effect size) are also given. Bold indicates a difference of more than 25%, red indicates the effect sizes are classified differently.*

	Total group	C/C variant	T/T variant	Comparison of

		group	group	effect size of C/C variant and T/T variant
Childhood trauma	t(67) = 2.389 p = .020 β = .282 R^2 = .080	**t(33) = 1.827** **p = .077** **β = .307** **R^2 = .094**	t(33) = 1.494 p = .145 β = .255 R^2 = .065	17% moderate vs. small
Recent life events	t(67) = .083 p = .934 β = .010 R^2 = .000	t(33) = .075 p = .941 β = .013 R^2 = .000	t(33) = -.020 p = .984 β = -.004 R^2 = .000	**131%** **trivial**
Recent daily hassles	t(67) = .898 p = .372 β = .110 R^2 = .012	t(33) = .829 p = .413 β = .145 R^2 = .021	t(33) = .384 p = .703 β = .068 R^2 = .005	**53%** **small vs.** **trivial**
Neuroticism	**t(67) = 3.098** **p = .003** **β = .356** **R^2 = .127**	**t(33) = 2.654** **p = .012** **β = .425** **R^2 = .180**	t(33) = 1.603 p = .119 β = .273 R^2 = .074	**36%** **moderate vs.** **small**
Working memory	t(67) = -1.495 p = .140 β = -.033 R^2 = -.181	**t(33) = -2.570** **p = .015** **β = -.414** **R^2 = .171**	t(33) = .458 p = .650 β = .081 R^2 = .007	**120%** **moderate vs.** **trivial**
IQ	**t(67) = -2.629** **p = .011** **β = -.308** **R^2 = .095**	**t(33) = -2.345** **p = .025** **β = -.383** **R^2 = .147**	t(33) = -1.268 p = .214 β = -.219 R^2 = .048	**43%** **moderate vs.** **small**

Table 2c. *The results of regression analyses done to determine the influence of variables on disorganized schizotypal symptoms. Bold and red indicates an effect size of .30 or larger (medium and up;(Cohen, 1992)). Comparisons of the effect size (difference divided by largest effect size) are also given. Bold indicates a difference of more than 25%, red indicates the effect sizes are classified differently.*

	Total group	C/C variant group	T/T variant group	Comparison of effect size of C/C variant and T/T variant
Childhood trauma	t(67) = 1.476 p = .145 β = .179 R^2 = .032	t(33) = .955 p = .347 β = .166 R^2 = .028	t(33) = 1.124 p = .269 β = .195 R^2 = .038	15%
Recent life events	t(67) = 1.155 p = .252 β = .141 R^2 = .020	t(33) = 1.024 p = .314 β = .178 R^2 = .032	t(33) = .453 p = .653 β = .080 R^2 = .006	**55%** **small vs.** **trivial**

Recent daily hassles	t(67) = 2.521 p = .014 β = .296 R^2 = .088	t(33) = 1.331 p = .192 β = .229 R^2 =.052	**t(33) = 2.107** **p = .043** **β = .349** **R^2 =.122**	**34%** **small vs.** **moderate**
Neuroticism	t(67) = 2.025 p = .047 β = .242 R^2 = .059	t(33) = 1.109 p = .276 β = .192 R^2 = .037	**t(33) = 1.887** **p = .068** **β = .316** **R^2 = .100**	**39%** **small vs.** **moderate**
Working memory	t(67) = -1.570 p = .121 β = -.190 R^2 = .036	**t(33) = -3.116** **p = .004** **β = -.483** **R^2 = .233**	t(33) = .606 p = .549 β = .106 R^2 = .011	**122%** **moderate vs.** **small**
IQ	t(67) = -1.298 p = .199 β = -.158 R^2 = .025	**t(33) = -1.837** **p = .075** **β = -.309** **R^2 = .095**	t(33) = -.037 p = .970 β = -.007 R^2 = .000	**98%** **moderate vs.** **trivial**

Table 2d. *The results of regression analyses done to determine the influence of variables on total schizotypal symptoms. Bold and red indicates an effect size of .30 or larger (medium and up; (Cohen, 1992)). Comparisons of the effect size (difference divided by largest effect size) are also given. Bold indicates a difference of more than 25%, red indicates the effect sizes are classified differently.*

	Total group	C/C variant group	T/T variant group	Comparison of effect size of C/C variant and T/T variant
Childhood trauma	**t(67) = 3.178** **p = .002** **β = .364** **R^2 = .133**	**t(33) = 1.875** **p = .070** **β = .315** **R^2 = .099**	**t(33) = 2.711** **p = .011** **β = .432** **R^2 = .187**	**27%** **moderate**
Recent life events	t(67) = .996 p = .323 β = .122 R^2 = .015	t(33) = .730 p = .471 β = .128 R^2 = .016	t(33) = .519 p = .607 β = .091 R^2 = .008	**29%** **small vs.** **trivial**
Recent daily hassles	**t(67) = 2.671** **p = .010** **β = .312** **R^2 = .098**	t(33) = 1.246 p = .222 β = .215 R^2 = .046	**t(33) = 2.574** **p = .015** **β = .414** **R^2 = .172**	**48%** **small vs.** **moderate**
Neuroticism	**t(67) = 2.921** **p = .005** **β = .338** **R^2 = .115**	**t(33) = 1.869** **p = .071** **β = .314** **R^2 = .098**	**t(33) = 2.392** **p = .023** **β = .389** **R^2 = .152**	19%
Working memory	t(67) = -1.654 p = .103 β = -.199 R^2 = .040	**t(33) = -3.021** **p = .005** **β = -.471** **R^2 = .222**	t(33) = .691 p = .495 β = .121 R^2 = .015	**126%** **moderate vs.** **small**

IQ	t(67) = -2.104 p = .039 β = -.251 R^2 = .063	**t(33) = -2.088** **p = .045** **β = -.346** **R^2 = .120**	t(33) = -.898 p = .376 β = -.157 R^2 = .025	**55%** **moderate vs.** **small**

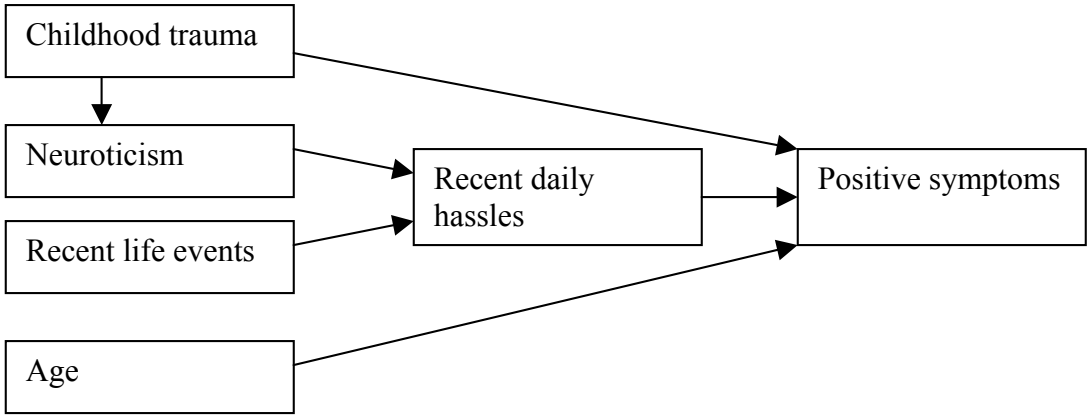

***Figure 9*. The best fitted data driven model, for the complete group, leading to positive symptoms. CFI: 1.000, RMSEA: 0.000, R^2 = .272**

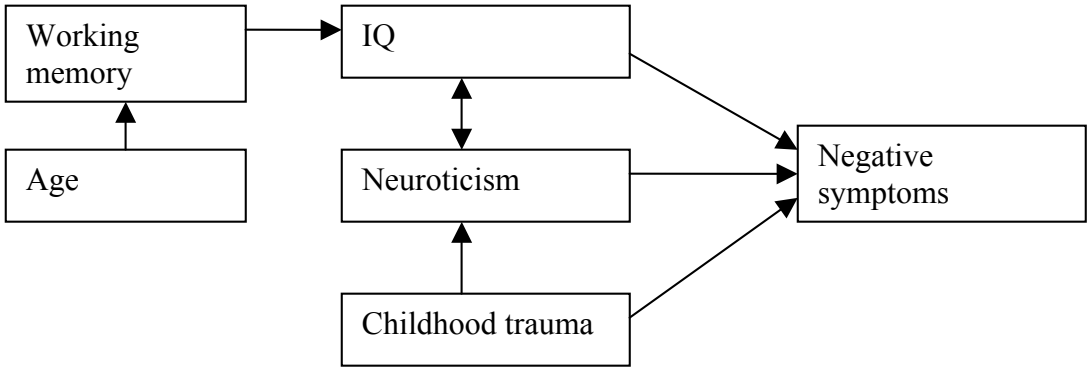

***Figure 10*. The best fitted data driven model, for the complete group, leading to negative symptoms. CFI: .992, RMSEA: .029, R^2 = .185**

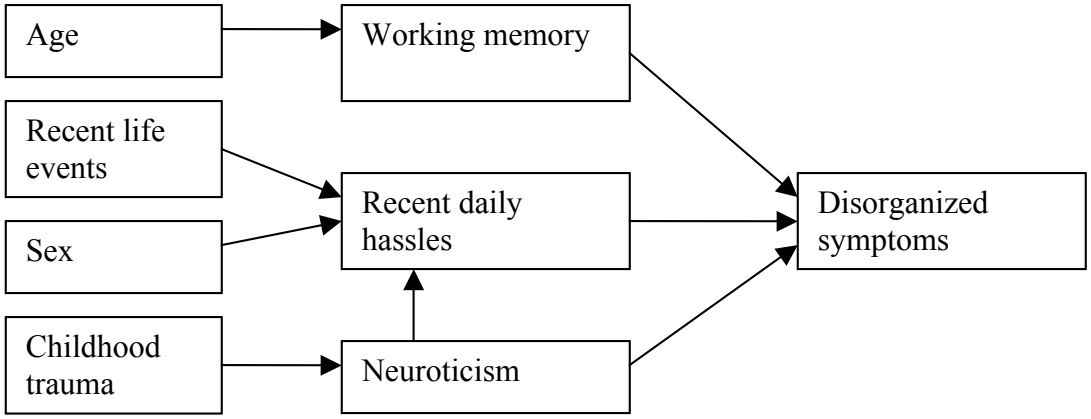

***Figure 11*. The best fitted data driven model, for the complete group, leading to disorganized symptoms. CFI: 1.000, RMSEA: 0.000, R^2 = .130**

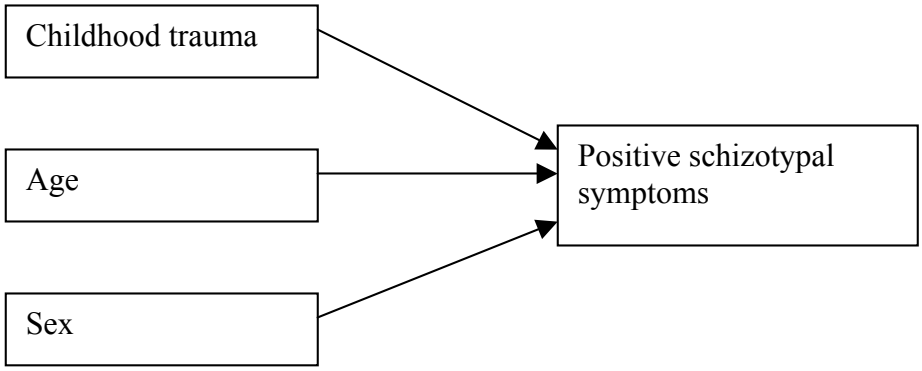

***Figure 12.* The best fitted data driven model, for the participants with the C/C variant, leading to positive symptoms. CFI: 1.000, RMSEA: 0.000, R^2 = .194**

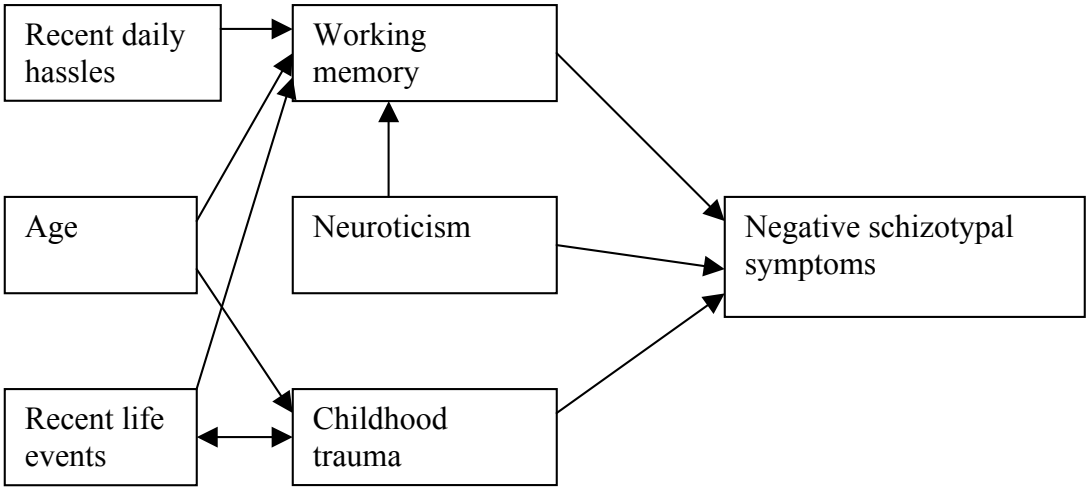

Figure 13. **The best fitted data driven model, for the participants with the C/C variant, leading to negative symptoms. CFI: 1.000, RMSEA: 0.000. R^2 = .286**

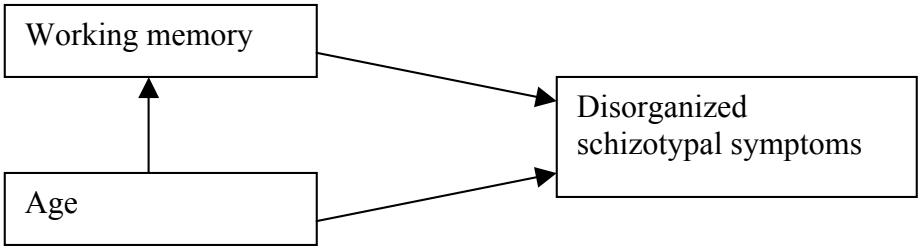

Figure 14. **The best fitted data driven model, for the participants with the C/C variant, leading to disorganized symptoms. CFI: 1.000, RMSEA: 0.000, R^2 = .299**

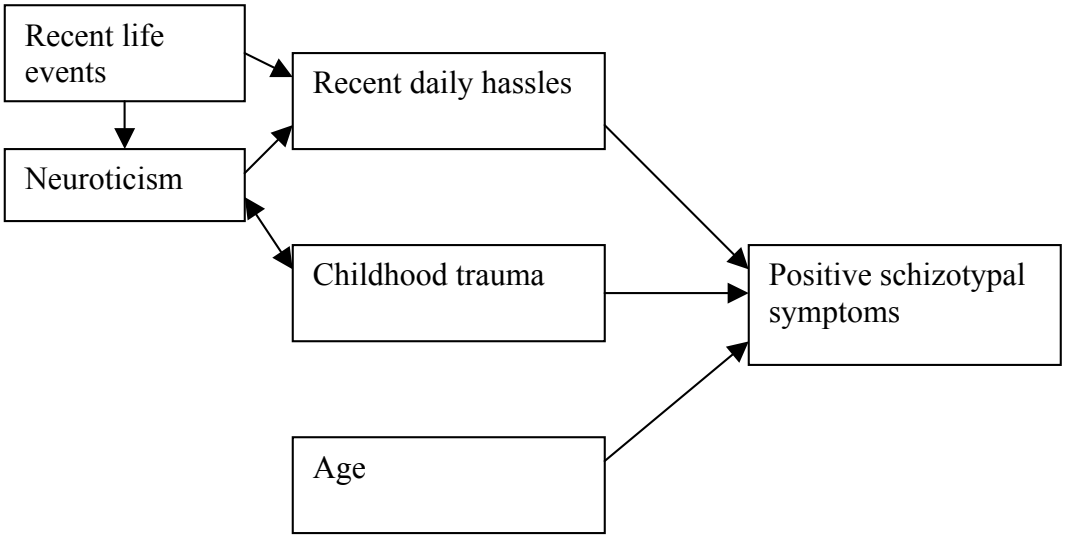

Figure 15. **The best fitted data driven model, for the participants with the T/T variant, leading to positive symptoms. CFI: 1.000, RMSEA: 0.000. R^2 = .534**

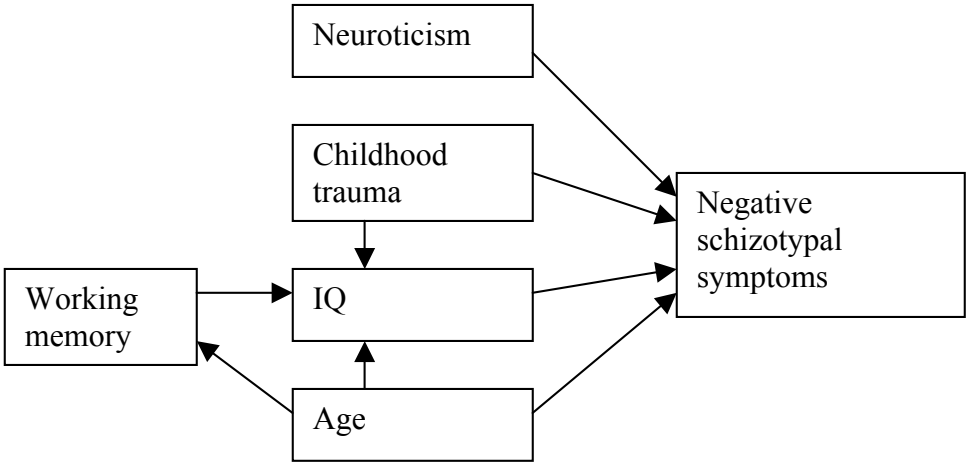

Figure 16. **The best fitted data driven model, for the participants with the T/T variant, leading to negative symptoms. CFI: 1.000, RMSEA: 0.000. R^2 = .209**

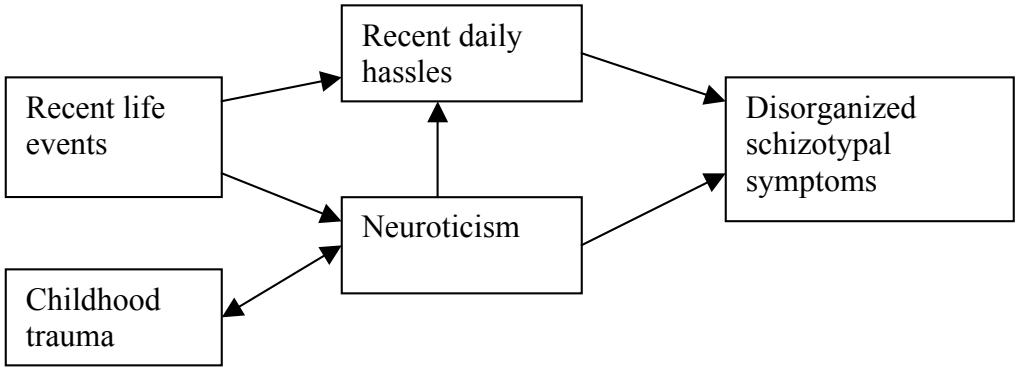

Figure 17. **The best fitted data driven model, for the participants with the T/T variant, leading to disorganized symptoms. CFI: 1.000, RMSEA: 0.000. R^2 = .161**

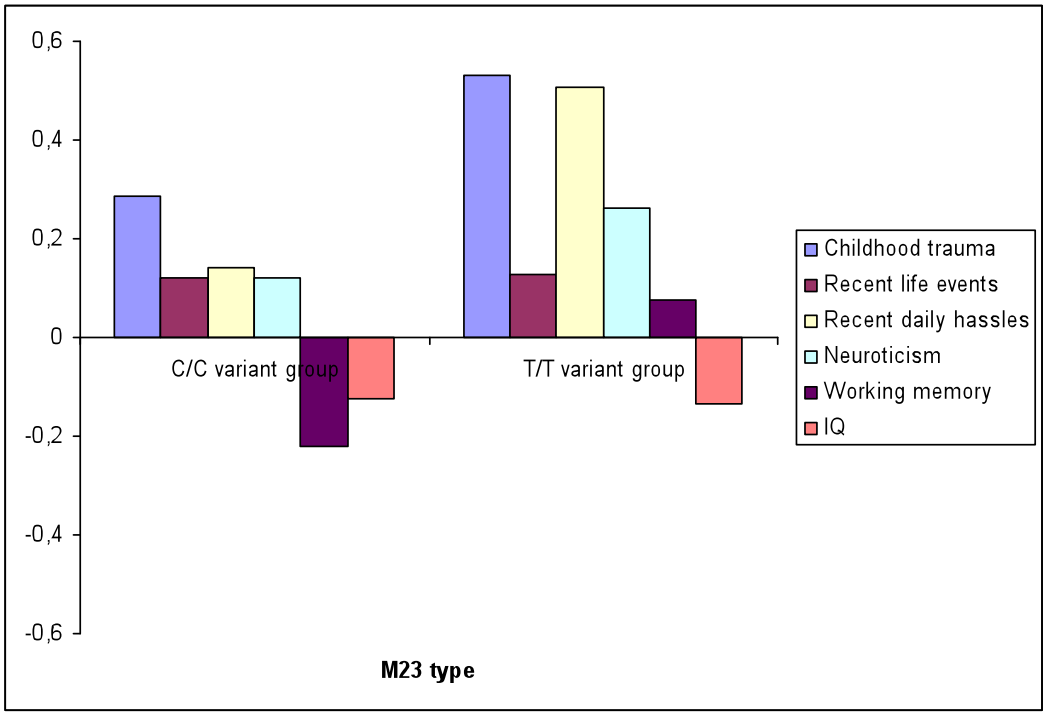

Figure 18. **Effect sizes of variables on positive schizotypal symptoms, for the group with M23 variant C/C and M23 variant T/T.**

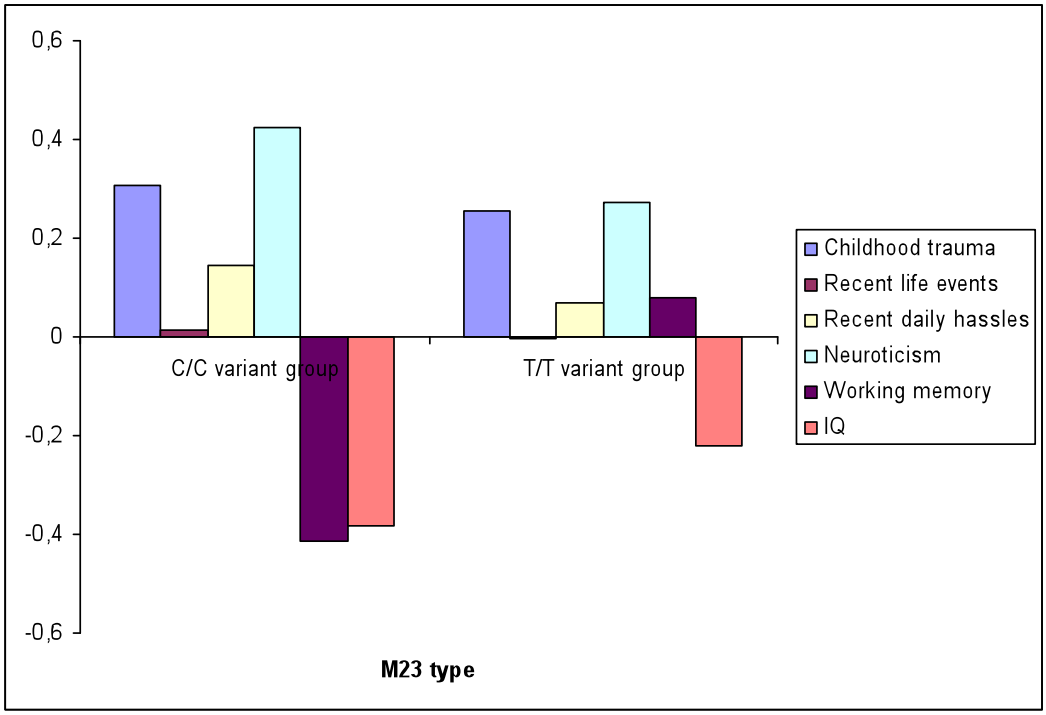

Figure 19. **Effect sizes of variables on negative schizotypal symptoms, for the group with M23 variant C/C and M23 variant T/T.**

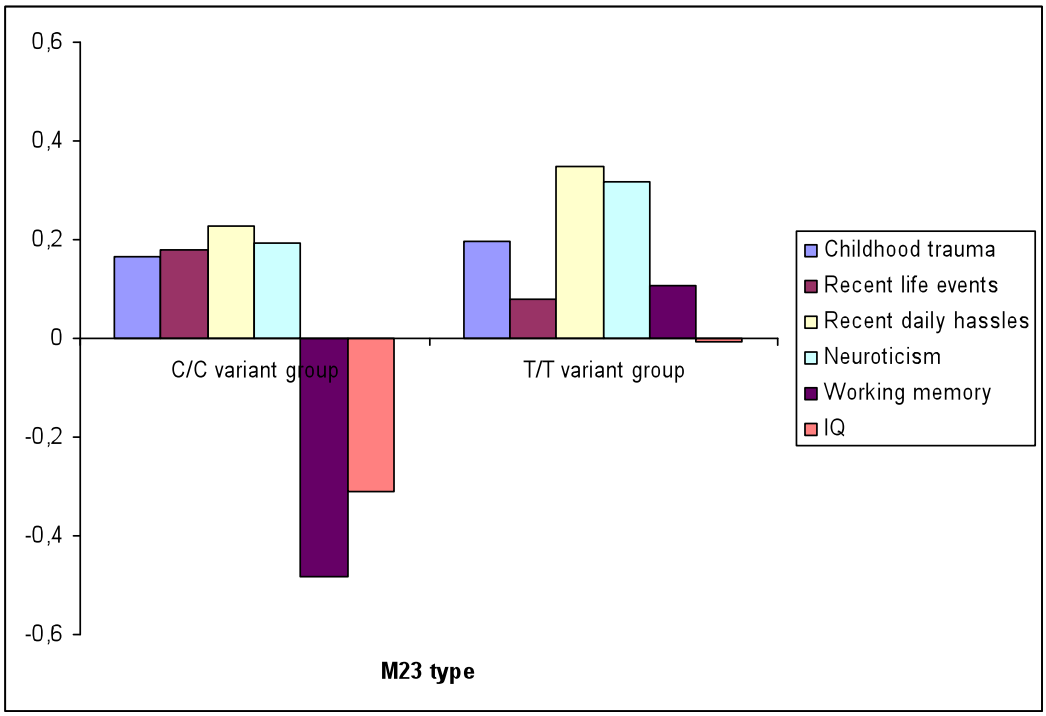

***Figure 20*. Effect sizes of variables on disorganized schizotypal symptoms, for the group with M23 variant C/C and M23 variant T/T.**

ADDENDUM 2: The questionnaires

Some items of each questionnaire are made available. They are in Dutch, since the questionnaires themselves were administered in Dutch as well.

Examples Childhood Trauma Questionnaire:

In mijn jeugd…

- Had ik niet voldoende te eten.
- Waren mijn ouders te dronken of stoned (onder invloed van drugs) om voor het gezin te zorgen.
- Was er iemand in mijn gezin die mij het gevoel gaf dat ik belangrijk en bijzonder was.

Answer options: Nooit waar / Zelden waar / Soms waar / Vaak waar / Zeer vaak waar

Examples Recent Life Events:

Is dit u in de afgelopen 12 maanden overkomen?

- U bent ernstig ziek geworden.
- Een van uw ouders, een kind van u of uw partner is overleden.
- U bent gescheiden als gevolg van huwelijksproblemen.

Answer options: Ja / Nee

Examples Recent Health Questionnaire:

In welke mate hebt u met de volgende aspecten moeilijkheden en stress (gehad) in de afgelopen 12 maanden?

- Uw partnerrelatie (vb: jaloezie, conflicten, twijfel aan relatie, ruzies)
- Met vrije tijd (vb: te weinig, te veel vrije tijd)
- Met financiën (vb: grote schulden, ontoereikend inkomen)

Answer options: niet stressvol / enigszins stressvol / zeer stressvol

Examples NEO-PI-R

- Ik ben geen tobber.

- Ik voel me vaak gespannen en zenuwachtig.
- Soms komen er angstaanjagende gedachten bij mij op.

Answer options: Helemaal oneens / Oneens / Neutraal / Eens / Helemaal eens

Examples Schizotypal Personality Questionnaire

- Ik heb geen expressieve en levendige manier van spreken.
- Maakt u zich wel eens zorgen over het feit dat vrienden of collega's niet loyaal of betrouwbaar zijn?
- Heeft u ooit dingen gezien die onzichtbaar waren voor andere mensen?

Answer options: Ja / Nee