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Genetic Covariation Underlying Reading, Language and Related Measures in a Sample Selected for Specific Language Impairment

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Abstract

Specific language impairment is a developmental language disorder characterized by failure to develop language normally in the absence of a specific cause. Previous twin studies have

documented the heritability of reading and language measures as well as the genetic correlation between those measures. This paper presents results from an alternative to the classical twin designs by estimating heritability from extended pedigrees. These pedigrees were previously studied as part of series of molecular genetic studies of specific language impairment where the strongest genetic findings were with reading phenotypes rather than language despite selecting pedigrees based on language impairments. To explore the relationship between reading and language in these pedigrees, variance components estimates of heritability of reading and language measures were conducted showing general agreement with the twin literature, as were genetics correlations between reading and language. Phonological short-term memory, phonological awareness and auditory processing were evaluated as candidate mediators of the reading-language genetic correlations. Only phonological awareness showed significant genetic correlations with all reading measures and several language measures while phonological short-term memory and auditory processing did not.

Keywords

Specific language impairment; Heritability; Language; Reading; Pedigree

Introduction

Specific language impairment (SLI) is defined by the failure to develop spoken language at the expected rate in the absence of cognitive, neurological, or psychological explanations. SLI often co-occurs with specific reading disability (SRD), also referred to as dyslexia, which is a deficit in written language, including printed word recognition and use, given adequate instruction and a lack of general cognitive deficits. Estimates of comorbidity for SLI and SRD vary from between 25 and 75% (McArthur et al. 2000). In addition to the comorbid nature of language and reading deficits, studies of children with SLI and SRD suggest similar levels of impairment on other constructs, particularly phonological awareness (Kamhi and Catts 1986), phonological short-term memory (Gathercole et al. 1994; Snowling 1981), and auditory processing (Corriveau et al. 2007; Tallal et al. 1980).

In addition to phenotypic findings, the domains of reading and language have shown significant genetic correlations (Harlaar et al. 2008; Haworth et al. 2009). Although these relations have yet to be fully explored, the extant literature shows that reading and language ability each have strong genetic effects in multiple subdomains (Plomin and Kovas 2005). For one, several lines of investigation have suggested that reading deficits are related to language deficits via phonological skills (Bishop and Snowling 2004). Catts and co-workers (Catts et al. 2005) found that co-occurring deficits in reading, language, and phonological awareness were common prior to fourth grade, but after that point phonological skills show only subtle deficits in language impaired individuals compared to unimpaired children. Similar findings of Bishop et al. (Bishop et al. 2009) suggest that phonological deficits are more pronounced in children with co-occurring reading and language impairment compared to those children with only one type of impairment.

Performance on phonological short term memory is a strong diagnostic predictor of language impairment and has been shown to be genetically influenced (Bishop et al. 1996, 1999, 2004). This construct is typically assessed with a nonword repetition task. Additionally, heritability for reading difficulty is greater for children who perform poorly on nonword repetition tasks than those in the normal range on this task (Bishop 2001, 2004). Finally, auditory processing, typically assessed with a temporal order judgment task, has also been implicated as a strong predictor of both language and reading ability (Bishop et al. 1999; Corriveau et al. 2007), however, the genetic evidence is not as strong. Though the

study by Bishop et al. (1999) found that auditory processing skills differentiated children with SLI from those with typical language skills, the heritability estimates were small and nonsignificant.

While there is considerable evidence that SLI and more broadly defined language impairment (LI) have a genetic basis (Bishop et al. 1995; Lewis and Thompson 1992; Neils and Aram 1986; Rice et al. 1998; Stromswold 1998, 2000; Tallal et al. 1989; Tomblin 1989; Tomblin and Buckwalter 1998), no large effect genetic variants have been identified to date. This may imply that SLI has a complex genetic etiology. Nonetheless, recent studies have shown that well-defined chromosomal regions around three genes have modest effects on language ability and appear to be very common risk factors for SLI, also modulating language skills in the general population (Newbury et al. 2009; Vernes et al. 2009).

Though the individual impairments have been well studied with molecular genetics, the comorbidity between SLI and SRD is limited to a candidate gene study where SRD genes were tested in SLI (Rice et al. 2009), and a series of studies in which Bartlett and colleagues found strong evidence for linkage of a reading phenotype in their families ascertained for SLI (Bartlett et al. 2002, 2004). Though this finding could suggest that the families were exhibiting SLI as a result of comorbidity with SRD, recent work by Simmons et al. (2010) did not support this hypothesis. Specifically, when the sample was sub-grouped based on LI status, poor readers were quantitatively distinguished from strong readers. However, the converse was not true: when the sample was sub-grouped based on SRD status, poor language ability was not quantitatively distinguished from strong language ability. Genetic linkage analysis results showed that when reading ability was assumed to predict language ability, the linkage signal diminished to background noise.

This finding is thus inconsistent with the hypothesis that reading deficits were simply reflecting language deficits in this sample.

In sum, SLI and SRD show moderate to high levels of comorbidity in phenotypic studies of impairment, and both are characterized by poor phonological awareness, phonological short term memory, and auditory processing. Both quantitative genetics and molecular genetics have informed the study of the underlying constructs of SLI and SRD. Quantitative genetics studies show strong genetic correlations between reading and language impairment, and have also shown some significant relations with the same additional constructs found to be important in the phenotypic literature. However, the Simmons et al. study provides evidence that the relation between SLI and SRD is not as apparent in molecular genetics.

In the present study, motivated by findings from the Simmons et al. (2010) study, we attempt to reconcile the findings of the molecular genetics literature with those of the quantitative genetics literature. We conducted a quantitative genetics analysis as the sampling unit for a heritability analysis, the same extended pedigrees ascertained for multiple individuals with SLI as those in our recent molecular genetic study (Simmons et al. 2010).

Extended pedigrees have distinct advantages over nuclear families for estimation of variance components in a heritability analysis. Nuclear families cannot distinguish between additive genetic effects and additive common environment. Researchers therefore, use other terms for describing estimates of familial resemblance including familiarity, generalized heritability, or multifactorial heritability. Regardless of the term used, the measured quantity includes both genetic and common environmental effects and is essentially the highest possible estimate of genetic effects, with no recourse for discerning how overestimated the genetic effects are in actuality. In contrast, extended pedigrees allow for dissociation of common environmental effects from genetic effects since extended relatives do not

(necessarily) share a common environment. As a result of this, the covariances assuming a polygenic model are uniquely specified to partition genetic from environmental effects.

In this study, we used the variance components framework to examine the genetic correlations of reading and language skills and their relationship to phonological awareness, phonological short-term memory and auditory temporal processing. If findings of typical quantitative genetics studies were replicated in this sample of families selected for SLI, we would expect to find significant genetic correlations between reading and language. In addition, both reading and language should show significant genetic correlations with phonological awareness, phonological short-term memory and auditory processing.

Subjects and methods

Families and phenotypes

Families were ascertained through a proband with SLI, with the requirement that each family have at least one additional family member meeting the study criteria for SLI. The sample consisted of 16 extended Caucasian families from the US ($N = 12$) and Canada ($N = 4$) for a total of 471 subjects (332 with behavioral data). All subjects gave informed consent conforming to the guidelines for treatment of human subjects at Rutgers university prior to behavioral testing.

In order to be identified as an SLI proband, a person had to meet the following inclusionary/exclusionary criteria:

1. Spoken language quotient (SLQ) of ≤ 85 on the age appropriate version of the test of language development (test of adolescent language TOAL:2 (Hammil et al. 1987), or TOLDP:2 (Newcomer and Hammil 1988), or TOLDI:2 (Hammil and Newcomer 1988)).
2. Performance IQ (PIQ) ≥ 80 on the age appropriate version of the Wechsler intelligence test (Wechsler intelligence scale for children WISC (Wechsler 1974), or the Wechsler Intelligence Scale for Adults WAIS (Wechsler 1981), or the Wechsler preschool and primary scale of intelligence WIPPSI (Wechsler 1989), or the Wechsler abbreviated scale for intelligence WASI (Wechsler 1999). Also, SLQ was required to be equal to or less than PIQ, in cases where PIQ was < 85 .
3. Hearing within normal limits [positive identification of 500 Hz at 30 dB (SPL), and 1000, 2000, and 4000 Hz at 20 dB (SPL)].
4. No motor impairments or oral structural deviations affecting speech or non-speech movement of the articulators as assessed by a speech-language pathologist.
5. No history of autism or frank neurological disorders such as mental retardation, seizure disorder, or brain injury as determined from parental report.
6. Native English speaker with English as the primary language spoken at home.

Measures

All subjects were tested with a comprehensive battery administered by an experienced tester. Depending on the location of the family, participants were either tested at the research laboratory or in their own homes. Assessment tools included:

1. The age appropriate version of the test of language development (TOLD), which is a comprehensive test of language functioning that addresses specific subcomponents of both expressive and receptive language processes including

speaking (expressive language), listening (receptive language), and grammar (syntax).

2. The age appropriate Wechsler intelligence test. Only the performance (nonverbal) IQ (PIQ) was included.
3. Audiological screening (see proband criteria).
4. Woodcock reading mastery (Woodcock 1987) subtests of Word identification (single word reading), Word attack (single nonword decoding) and Passage comprehension (reading short passages and filling in a missing word from the end of the passage).
5. Test of auditory analysis skills (TAAS) (Rosner 1979). The TAAS is a measure of phonological awareness. In this test, subjects are presented with words orally and asked to delete a beginning sound, an ending sound, or a part of a blend.
6. The children's test of nonword repetition (CNRep) (Gathercole et al. 1994) is a measure of phonological memory. The test requires a subject to repeat verbatim non-words presented on audio tape. Non-words are strings of phonemes that are phonologically possible in English, but are not real English words (such as "blonterstaping" or "woogalamik").
7. Auditory repetition test (ART) (Tallal and Piercy 1973a), included as a measure of temporal auditory processing, is an operantly trained method for assessing the processing of 2 and 3 tone sequences presented rapidly in succession (75 ms duration complex tones, fundamental frequency of 100 or 300 Hz, interstimulus intervals 10 or 70 ms). The quantitative outcome applied in this study was the percent correct for the 2 and 3 tone presentations. This test measures the subject's ability to perceive brief, rapidly presented frequency changes over time, which has been hypothesized to play an important role in processing of rapidly changing frequency cues within some speech stimuli (Tallal and Piercy 1973a, b, 1974, 1975; Tallal et al. 1998).

Statistical analysis

Estimates of additive genetic heritability for quantitative traits were calculated by the SOLAR package v4.2 (Almasy and Blangero 1998) using a maximum likelihood algorithm to decompose the components of variance (additive genetic versus non-additive genetic and environmental). This technique uses genetic information from the entire pedigree by considering all possible relative pairs jointly. Of the 332 participants who had behavioral data, the number of phenotyped relative pairs that were informative for heritability calculations ranged from 1468 to 1870. Not all subjects completed all tests. Most missing data were from the reading tests and the auditory processing measure since several younger children could not take these measures. The number of relative pairs used for each analysis is presented as an index to the complexity of the pedigrees and describes the relative power of the sample.

Only narrow sense heritability is presented in this paper as only a few extended familial relationships (such as full sibling pairs or double first cousin pairs) are capable of providing information about dominance in outbred populations that exhibit considerable genetic diversity (Jacquard 1974).

As variance components can be sensitive to departures from multivariate normality, particularly kurtotic distributions, we have employed the robust estimator assuming the multivariate-*t* distribution when kurtosis is >1.5 as recommended (Allison et al. 1999; Blangero et al. 2000). The multivariate-*t* distribution down weights values that are extreme

with regard to the multivariate normal. It should be noted that the robust estimator is not required for parameter estimation, which is generally reasonable with regard to estimated magnitude (Rao et al. 1987), but is necessary for a valid statistical test of hypothesis.

Significance tests of estimated parameters are generated by comparing the likelihood of the genetic model when the estimated heritability constrained between zero and one, versus the likelihood of a genetic model with the heritability constrained to zero. This is a likelihood ratio test with a mixed distribution of a Chi-square and a point mass of zero (Self and Liang 1987). In place of confidence intervals, standard errors were derived by inversion of Fisher's information matrix.

For each obtained genetic and shared environment estimate and correlation, performance IQ (PIQ), age, gender, and the interaction of age by gender were tested as covariates in the model. This was accomplished by calculating the likelihood with and without the covariate and performing a likelihood ratio test. All covariates that were significant at $P < 0.05$ were kept in the model.

Results

Table 1 summarizes the sample's descriptive statistics. The descriptive statistics show the extremity of the ascertainment of probands relative to the sample as a whole. Included in Table 1 are the central moments calculated from the data as a general indicator of normality. Table 2 summarizes the univariate heritability estimates for the language, reading, phonological awareness, phonological short-term memory, and auditory processing (temporal order judgment) skills tested, and the covariates accounted for each of these. All measures showed significant heritability after correction for multiple tests.

The first goal of the study was to examine the significance of the genetic and shared environmental correlations between the reading and language skills assessed. These are presented in Table 3. Though three subtests of the TOLD were given, only the overall standard score is reported in Table 3. It should be noted that the significance patterns for the subtests of the TOLD were consistent with that of the overall standard score unless otherwise indicated below.

As expected, all language measures derived from the TOLD showed significant genetic correlations with all tests given as part of the Woodcock reading mastery test (Word attack, Word ID, Passage comprehension). There were significant shared environmental correlations observed between the TOLD standard score and both Word attack and Passage comprehension, but not Word identification. However, there was a significant shared environmental correlation observed between Word identification and the grammar subtest of the TOLD (0.69; $P < 0.01$). In addition, no significant shared environmental correlations were observed between the three reading measures and the receptive language subtest of the TOLD (all P -values > 0.05).

The second goal was to examine the genetic overlap between reading and phonological skills and between language and phonological skills. As expected, there were significant genetic correlations between TAAS and all three reading measures (TAAS-Word ID, 0.64, $P < 0.001$; TAAS-Word attack, 0.66, $P < 0.01$; TAAS-Passage comprehension, 0.68, $P < 0.01$). The only significant environmental correlation of phonological awareness with reading was that between the TAAS and Word attack (0.28, $P < 0.01$).

Contrary to our original prediction, other results were more mixed. Although there was no significant genetic or shared environmental overlap observed between the TAAS and overall language skills as measured by the TOLD (see Table 3), there was a significant genetic

correlation observed between the TAAS and the expressive language subtest (0.52; $P < 0.01$). In addition, there were significant shared environmental correlations observed between the TAAS and both receptive language (0.40; $P < 0.01$) and grammar (0.27; $P < 0.05$).

Also, phonological short term memory, as measured by the CNRep, was not significantly genetically correlated with any measures of reading or with language skills overall and there was no significant environmental correlation with any of the reading measures (Table 3). However, there was a significant environmental correlation with overall language measures (TOLD 0.38; $P < 0.01$). In addition, the CNRep showed both significant genetic (0.84; $P < 0.05$) and environmental (0.28; $P < 0.01$) correlations with the TAAS. Finally, the auditory repetition test (Tallal and Piercy 1973a) showed a significant positive genetic correlation (0.55; $P < 0.05$) and negative environmental correlation (-0.58 ; $P < 0.05$) with Word ID. No significant correlations were observed between the ART and the language measure. However, the ART and CNRep tests showed a significant environmental correlation (0.54; $P < 0.001$).

Discussion

The present study is one of the first studies to combine the statistical methodologies of molecular and quantitative genetics. Through these methods, we were able to obtain sample-based estimates of heritability and shared environment, as well as genetic and environmental correlations between reading, language, and three proposed underlying constructs. Strong genetic correlations were observed between language and reading measures in our extended families ascertained for SLI, in agreement with previous studies (Stromswold 2001). In addition, marginal environmental correlations were observed, although these were not consistent across all reading and language measure combinations.

The three components tested for genetic correlation with reading and language ability were phonological short-term memory, auditory processing and phonological awareness. The first component, phonological short-term memory (CNRep), has been found to predict language and reading ability and has been hypothesized to affect language and reading by modulating capacity for phonological processing (Bishop et al. 1999; Corriveau et al. 2007). Though the results of the present study did show significant genetic and environmental correlations of phonological memory with phonological awareness, no significant genetic correlations were observed between phonological short-term memory and either reading or language. This suggests that expressive skills such as speaking and sentence production rely heavily on phonological processes such as phonological and phonetic encoding as well as articulatory-motor preparation (reviewed in Schiller et al. 2006).

For the second component examined, auditory processing, past quantitative genetics studies have not found significant relations of reading or language with temporal order judgment tasks including the ART (Bishop et al. 1999). However, it was hypothesized that in a pedigree selected for SLI these relationships may have been important. Contrary to this hypothesis and in line with the previous literature, no significant genetic or shared environmental correlations of reading or language with the ART were found.

The third construct thought to underlie aspects of both reading and language skills is phonological awareness, previously shown to be impaired in those readers with SLI and those with SRD (Catts et al. 2005; Kamhi and Catts 1986). In addition, phonological awareness has been shown to share significant genetic variance with reading and language skills in both selected and unselected samples (Bates et al. 2007; Kovas et al. 2005; Olson et al. 1989). In the present study, we found some evidence aligned with these prior findings,

but results related to phonological awareness showed some specificity for the particular aspects of reading and language measured.

First, we consider the relations of phonological awareness with outcomes related to language use and processing. The covariance of phonological awareness with measures of receptive language and grammar showed significant shared environmental influences (but not significant genetic influences). This raises some questions about the source of those common shared environmental influences, which could include experience with language, similar school environments, similar geographical locations of the families, or socio-economic status. Any of these sources of variance have potential to be explained if shared environments are measured adequately. Thus, this finding provides an interesting direction for future studies. The covariance between phonological awareness and expressive language was attributable to genetic influences. This finding aligns with currently held models of speech production, which suggest that expressive language is highly dependent on the phonological system [Levelt et al. (1999) for an explanation of one current theoretical model]. Thus, the present findings provide a step towards understanding how theoretical models of language use and processing can be explained in terms of genetic etiology.

Turning to reading, the underlying covariance of phonological awareness with each of the three measured aspects of the reading process (decoding, word reading, and reading comprehension) was explained by genetic differences within the sample. This is directly in line with previous genetic findings of reading and phonological awareness (Petrill et al. 2006). On the environmental side, only the correlation of phonological awareness with nonword decoding was significantly attributable to both genetics and environmental influences. This is in contrast to previous studies, which show significant shared environmental influences on the covariance of phonological awareness with Word identification (Petrill et al. 2006) and reading comprehension (Byrne et al. 2005). The difference between the findings of the present study and those reported previously is likely a result of unique sample characteristics; this study used multiple age groups, and thus had increased environmental diversity compared to traditional behavioral genetics studies.

Many, perhaps most, studies on the heritability of reading, language, and related components have estimated heritability in a single restricted age range. In contrast, this study used several different age groups jointly. There is some evidence that heritability of performance on language and reading measures changes depending on age. For example, genetic effects on phonological outcomes tend to become increasingly more important as children age (Byrne et al. 2005). However, environmental influences appear to be consistently important across childhood for real word reading ability (Petrill et al. 2007). In addition, general cognitive ability has been shown to change throughout the lifespan (Haworth et al. 2010). Therefore, estimates of univariate heritability observed in the present study may have differed from those reported in the previous studies. However, the magnitude of our univariate heritability estimates is similar to those from previous work on language (Stromswold 2001), as well as reading ability, including decoding (accurate reading of non-words) and orthography (knowledge of correct spellings of real words), for which these estimates are at or above 0.65 (Gayan and Olson 2003; Harlaar et al. 2007).

Data from multiple age groups could also have had an impact on the observed genetic and environmental correlations. Though strong genetic correlations were observed between reading and language in a very large population based sample (Harlaar et al. 2008), the results suggested that more of the correlation between reading and language achievement was due to the shared environment. In the Harlaar et al. study, the authors decomposed correlations in measures of expressive vocabulary and syntax at ages 2–4 with standardized reading achievement tests at ages 7, 9 and 10. Of the reading measures used in the present

study, Passage comprehension is the closest to the material found on a standardized test. However, since the reading achievement scores include much variance not attributable to comprehension, it is unclear how to compare the two studies more directly. Therefore, while the multiple ages in the sample of the present study are one explanation for the observed effect, alternative explanations cannot be ruled out as the two studies are not directly comparable.

In addition, it should be noted that the results of the present study can only be generalized to the population and constructs examined. We examined reading (including decoding, word recognition, and comprehension) of printed English words, the comprehension of spoken English language, and speech production. These results do not inform the discussion about other aspects of reading (i.e. fluency or inference making) or language (i.e. lexical stress or morphology), nor are they generalizable to languages other than English.

In summary, the results of this study demonstrated significant relationships of reading and language with phonological awareness, but not for the other two candidates thought to underlie this relation (phonological memory and auditory repetition). Overall, the results of this genetically restricted sample yielded similar genetic and environmental estimates to previous quantitative genetics studies of reading and language and their underlying constructs. These findings can be used to inform the discussion of cognitive models of reading and language use and processing.

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Table 1

Descriptive statistics

Test	Group	Mean	SD	Skewness	Kurtosis	n
Performance IQ	Sample	103.68	13.59	-0.14	0.24	270
	Proband	101.57	7.78	-1.21	-0.59	14
Spoken language quotient (TOLD)	Sample	96.24	16.70	-0.34	0.16	187
	Proband	80.00	13.28	1.50	2.35	14
Expressive language	Sample	99.89	19.26	-0.77	0.56	187
	Proband	77.40	8.26	-1.00	-0.43	14
Receptive language	Sample	100.59	17.37	-0.47	-0.04	187
	Proband	80.4	8.08	0.99	1.09	14
Word identification	Sample	97.71	12.93	-0.85	1.68	259
	Proband	82.94	18.38	-0.73	0.61	14
Word attack	Sample	98.12	14.97	-0.16	0.29	259
	Proband	84.78	14.67	-0.14	-0.57	14
Passage comprehension	Sample	99.09	14.85	-0.26	0.78	256
	Proband	89.14	15.30	-0.41	-0.92	14
Test of auditory analysis skills	Sample	10.18	3.34	-1.25	0.48	259
	Proband	9.9	3.69	-1.02	-0.92	14
Children's nonword repetition test	Sample	93.01	13.24	-2.48	7.85	199
	Proband	79.3	28.01	-1.97	4.67	14
Auditory repetition test	Sample	86.76	15.47	-0.79	1.80	243
	Proband	76.08	16.11	0.39	-1.15	14

Table 2

Heritability of language and reading tests

Skills assessed	Test	h^2	Standard error	P-value	Covariates
Language-related	Performance IQ	0.53	0.10	<0.0001	Age
	Spoken language quotient	0.46	0.12	<0.0001	Age, sex, PIQ
	Expressive language	0.40	0.12	<0.0001	PIQ
	Receptive language	0.50	0.14	<0.001	Sex, PIQ
Reading	Word identification	0.86	0.08	<0.0001	PIQ
	Word attack	0.55	0.11	<0.0001	PIQ
	Passage comprehension	0.53	0.12	<0.0001	PIQ
Phonological	Test of auditory analysis skills	0.23	0.11	<0.01	Age, sex, PIQ
	Children's nonword repetition test	0.36	0.07	<0.0001	Age, PIQ
	Auditory repetition test	0.49	0.12	<0.0001	Handedness

Table 3

Genetic and environmental correlations of language, reading and phonology

	Language-related processes			Phonological awareness			Reading skills			
	TOLD			TAAS			WA			
	ρ_G	ρ_E	ρ_G	ρ_G	ρ_E	ρ_G	ρ_G	ρ_E	ρ_G	ρ_E
TOLD	–	–	±0.27	±0.09	±0.14	±0.14	±0.07	±0.19	±0.13	±0.14
TAAS	0.41	0.10	–	–	±0.24	±0.10	±0.18	±0.19	±0.22	±0.11
WA	0.56**	0.36*	0.66*	0.28*	–	–	±0.03	±0.22	±0.02	±0.05
WID	0.82*****	0.39	0.64**	0.16	0.92*****	0.28	–	–	±0.03	±0.25
PASS	0.60**	0.35*	0.68*	0.16	0.95*****	0.80*****	0.92*****	0.20	–	–

In the *lower left triangle* are the genetic and environmental correlations while in the *upper right triangle* are the corresponding standard errors enclosed in *parentheses*

* $P < 0.05$,

** $P < 0.01$,

*** $P < 0.001$,

**** $P < 0.0001$

TOLD Test of oral language development (TOLD) spoken language quotient, TAAS Test of auditory skills analysis, WA Word attack, WID Word identification, PASS Passage comprehension

ρ_G Genetic correlation

ρ_E Environmental correlation