Final Report and Summary for
'Effects of Genetic Variation in Dopamine on Language'
5R03HD50671-2
PI: Ganger, Jennifer B.

Background

The aims of this work are (1) to test whether genetic evidence supports a distinction between declarative memory and computational procedures within cognition (per'dual-system' models, specifically the 'declarative-procedural' model) and (2) to identify which genes are associated with these processes.

The declarative-procedural distinction was tested using an established, well-understood psycholinguistic paradigm: the elicited production of regular and irregular past tense forms. Evidence from a variety of sources suggests that regular past-tense forms are affixed in a rule-governed manner (stem + -ed, e.g, *walked*) and thus can be composed by procedure using the mental grammar. Irregular past-tense forms, on the other hand, are at least partly idiosyncratic (e.g,. *dig-dug*), and thus must depend on representations stored in lexical memory, which in turn appears to depend on the declarative memory system (Ullman, 2001, 2004).

One of the main lines of evidence for this distinction comes from the examination of past-tense frequency effects. Frequency effects are shown when forms with a higher frequency of occurrence in the language are processed more quickly and accurately than lower frequency forms. Irregular past tenses typically show the frequency effect (e.g., higher frequency irregular past tenses are processed faster than lower frequency irregular past tenses), indicating they are stored as full forms. In contrast, regular past tenses do not show such a full-form frequency effect, indicating that they are not accessed as full forms in memory, but are rather likely to be composed each time they are produced (i.e., *walk* + *-ed*). Thus, frequency effects for inflected forms (i.e., past tense forms such as *walked* and *dug*) are taken as a diagnostic for storage, as opposed to composition, if one holds potentially confounding factors constant. Importantly, although regulars can and often are composed, they can also be stored, which can be detected by frequency effects. The storage (versus composition) of regulars has been shown to be affected by various subject- and item-level factors, including subject-level factors leading to superior declarative memory abilities (Ullman, 2004, 2007, In Press 2008; Ullman, Miranda, & Travers, 2008).

A Promising New Hypothesis

The proposal for this work called for an association study with dopamine-related genes, a hypothesis that stemmed from previous work in neuroscience and neuropsychology (Ullman, 2004; DeFrias et al., 2004; DiMaio, Grizenko & Joober, 2003; Nieoullon, 2002; Schultz, 2001; Meador-Woodruff, 1998; Gerfen, 1995; Yebenes & Gomez, 1993; Goldman-Rakic et al., 1992). Although the original hypothesis remains intact and will be tested in the upcoming months, we began our analysis with another gene whose promise in contributing to our understanding of the dual-system model came to light only in the last few years: brain-derived neurotropin factor, or BDNF.

The gene for BDNF has a SNP (single nucleotide polymorphism) at codon 66 that changes the resulting amino acid from valine (val) to methionine (met). The val allele has been associated with superior declarative memory functionality (Dempster et al., 2005; Egan et al., 2003; Goldberg et al., 2007; Hariri et al., 2003; Ho et al., 2006), greater relative hippocampal volumes (Pezawas et al., 2004; Szeszko et al., 2005), and greater hippocampal activation in fMRI studies of declarative memory (Goldberg et al., 2007; Hariri et al., 2003; Hashimoto et al., in press; Pezawas et al., 2004), particularly in val/val homozygous individuals as compared to met homozygotes or heterozygotes (met/met or val/met).

This work led to a new hypothesis, one not included in our proposal: We predicted that BDNF would be associated with declarative memory in past tense production. Specifically, the val allele should be associated with stronger past-tense frequency effects for regulars, reflecting their greater likelihood of storage, as compared to the met allele, due to the val allele's association with better declarative memory. In contrast, such a val-met difference in frequency effects would not be expected for irregulars, since these must always be stored. Finally, we explored whether these BDNF alleles might interact with sex. The sex difference rests on evidence suggesting that females (Kramer, Delis, Kaplan, O'Donnell, & Prifitera, 1997; Maitland, Herlitz, Nyberg, Backman, & Nilsson, 2004; McGivern et al., 1997) show advantages in declarative memory compared to males (Alexander, Packard, & Peterson, 2002; Herlitz, Nilsson, & Backman, 1997; Kimura, 1999; Kramer, Delis, & Daniel, 1988; McGivern et al., 1997; Trahan & Quintana, 1990; Ullman et al., 2008).

Procedure

Over the period of the grant, behavioral, demographic, and genetic data were collected from more than 150 participants though Dr. Steve Manuck's Adult Health and Behavior (AHAB) project at the University of Pittsburgh. (More participants were included in the original plan, but the AHAB funds were depleted earlier than Dr. Manuck expected. See **Future Directions** below for more on this.) Dr. Ullman's lab has completed transcribing and coding the past tense production data from these subjects, and with the generous cooperation of Dr. Manuck's lab, genetic data have been made available on all of the dopamine alleles and BDNF alleles for these participants as well as many other genes that AHAB investigators were interested in.

Following the methodology of previous studies of past tense production carried out in Dr. Ullman's lab (e.g., Gelfand, Walenski, Moffa, Lee, & Ullman, Under Revision; Prado & Ullman, Under Review; Ullman et al., Under Revision; Walenski, Mostofsky, & Ullman, 2007), frequency effects were examined on response time data for correct first-responses to 58 English verbs (29 consistent regular, 29 irregular). Experimenter-noted timer errors and extreme outliers for each subject (RT's more than 3.5 standard deviations from the subject's mean) were excluded from analysis. Significance of all effects was assessed using $p = 0.05$. All p-values reported are two-tailed. In all analyses, degrees of freedom were computed using the Satterthwaite approximation. The response time data were analyzed using hierarchical linear modeling (HLM) with random effects of subject. This statistical method allows each individual response time from each subject and item to be entered into one model, without averaging response times, which results in

a substantial loss of information. HLM accounts for subject variability by including the baseline performance (model intercept) of each subject as a random variable.

An HLM model was constructed with natural logarithm-transformed response time as the dependent variable; past-tense frequency and verb-type (regular versus irregular) as item-level (level-1) variables; and BDNF (val/val versus val/met and met/met combined) and sex (male versus female) as subject-level (level-2) variables. Interactions were specified between BDNF, sex, verb-type, and frequency, generating separate frequency coefficients for each level of the BDNF by sex by verb-type interaction. Following previous studies, four potentially confounding variables were included as variables in the model: whether the verb begins with a fricative, whether the verb begins with a plosive, natural-log-transformed item order, and a measure of phonological neighborhood.

Included in this analysis are 157 subjects (86 males, 71 females; 146 white and 11 black; 28 30-to-39-year-olds, 77 40-to-49-year-olds, and 52 50-to-54-year-olds, with an overall mean age of 45.7 (SD=5.9).

Results

We focus on the contrasts which treat *val/met* individuals and *met/met* individuals as one group because this grouping has produced the most robust results in previous studies (Dempster et al., 2005; Egan et al., 2003; Goldberg et al., 2007; Hariri et al., 2003; Hashimoto et al., In press; Ho et al., 2006; Pezawas et al., 2004; Szeszko et al., 2005). That is, we contrasted met-carriers with *val/va*l homozygotes.

<u>*Main effect of BDNF alleles on frequency*</u>. As predicted, BDNF alleles were differentially associated with frequency effects, though the direction of the effect was unexpected. Despite previous evidence showing an association of val/val homozygotes with superior declarative memory, the *val/val* versus *met-carrier* comparison in this study linked the met allele to more pronounced frequency effects, over both verb-types and sexes (β = .008, t = 1.863, p = .063).

<u>*Interactions with sex and verb type.*</u> In typical male subjects, irregular verbs demonstrate a frequency effect (negative beta significantly different from zero) while regular verbs do not (beta not significantly different from zero); females in contrast may show frequency effects on regular items as well as irregular items, likely due to increased reliance on storage (as opposed to composition) of complex forms. Here, we are principally interested in any interactions with BDNF that suggest a departure from the typical pattern, as well as the lower-level effects that might help explain that interaction.

There was no two-way interaction between BDNF and verb-type with respect to frequency effects. Additionally, there was no three-way (BDNF by sex by verb-type) interaction with respect to frequency effects. However, the model yielded a significant interaction of BDNF by sex summing across the two verb-types (β = -.020, t = -2.182, p = .029). This effect appears to be driven by a particularly strong frequency effect on irregulars for met-carrier as compared to *val/va*l females.

Conclusions and Future Directions

The BDNF analysis proved extremely fruitful in achieving the goal of this study: using genetic evidence to reinforce the dual-system model. As expected, the BDNF alleles were differentially associated with frequency effects, and such a result is only

compatible with a theory that distinguishes between the two verb types . However, the pattern was not the one predicted, and further work is needed to understand why the direction of this effect is the reverse of that found in previous research (i.e., why *met* is associated with frequency effects in this study, while in previous research *val* has been associated with superior declarative memory).

In addition to continuing to explore the BDNF results, similar analyses are underway to test the dopamine genes specified in the original proposal. If the results continue to be promising, we will pursue further funding to continue the work. Dr. Manuck has recently secured more funding for the AHAB project and has already restarted it, suggesting a straightforward and efficient way for us to collect more data if we can secure more funds.

References

Alexander, G. M., Packard, M. G., & Peterson, B. S. (2002). Sex and spatial position effects on object location memory following intentional learning of object identities. *Neuropsychologia, 40*(8), 1516-1522.

Dempster, E., Toulopoulou, T., McDonald, C., Bramon, E., Walshe, M., Filbey, F., et al. (2005). Association Between BDNF Val66 Met Genotype and Episodic Memory. *American Journal of Medical Genetics Part (Neuropsychiatric Genetics), 134B*, 73-75.

De Frias C., Annerbrink K., Westberg L., Eriksson E., Adolfsson R., and Nilsson L. (2004) COMT Gene Polymorphism Is Associated with Declarative Memory in Adulthood and Old Age. Behav Genet. 34, p533-539.

DiMaio S., Grizenko N., and Joober R. (2003) Dopamine genes and attention-deficit hyperactivity disorder: a review. *J Psychiatry Neurosci*. 28, p27-38.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112*(2), 257-269.

Gelfand, M. P., Walenski, M., Moffa, M., Lee, S., & Ullman, M. T. (Under Revision). The Influence of Handedness on Language: Storage versus Composition Differences in Left- and Right-Handers.

Gerfen C. R. (1995) Dopamine receptor function in the basal ganglia. *Clin Neuropharmacol*. 18, S162-S177.

Goldberg, T. E., Iudicello, J., Russo, C., Elvevag, B., Straub, R., Egan, M. F., et al. (2007). BDNF Val^{66}Met polymorphism significantly affects d' in verbal recognition memory at short and long delays. *Biological Psychology, 77*(1).

Goldman-Rakic P. S., Lidow M. S., Smiley J. F., and Williams M. S. (1992) The anatomy of dopamine in monkey and human prefrontal cortex. *Journal of Neural Transmitters*. 36, 163-177.

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., et al. (2003). Brain-Derived Neurotrophic Factor val66met Polymorphism Affects Human Memory-Related Hippocampal Activity and Predicts Memory Performance. *Journal of Neuroscience, 23*(17), 6690-6694.

Hashimoto, R., Moriguchi, Y., Yamashita, F., Mori, T., Nemoto, K., Okada, T., et al. (In press). Dose-dependent effect of the Val66Met polymorphism of the brain-derived neurotropic factor gene on memory-related hippocampal activity. *Neuroscience Research*.

Herlitz, A., Nilsson, L. G., & Backman, L. (1997). Gender differences in episodic memory. *Memory and Cognition, 25*(6), 801-811.

Ho, B.-C., Milev, P., O'Leary, D. S., Librant, A., Andreasen, N. C., & Wassink, T. H. (2006). Cognitive and Magnetic Resonance Imaging Brain Morphometric Correlates of Brain-Derived Neurotrophic Factor Val66Met Gene Polymorphism in Patients With Schizophrenia and Healthy Volunteers. *Archives of General Psychiatry, 63*(7), 731-740.

Kimura, D. (1999). *Sex and cognition*. Cambridge, MA: The MIT Press.

Kramer, J. H., Delis, D. C., & Daniel, M. (1988). Sex differences in verbal learning. *Journal of Clinical Psychology, 44*(6), 907-915.

Kramer, J. H., Delis, D. C., Kaplan, E., O'Donnell, L., & Prifitera, A. (1997). Developmental sex differences in verbal learning. *Neuropsychology, 11*(4), 577-584.

Maitland, S. B., Herlitz, A., Nyberg, L., Backman, L., & Nilsson, L. G. (2004). Selective sex differences in declarative memory. *Memory and Cognition, 32*(7), 1160-1169.

McGivern, R. F., Huston, J. P., Byrd, D., King, T., Siegle, G. J., & Reilly, J. (1997). Sex differences in visual recognition memory: Support for a sex-related difference in attention in adults and children. *Brain and Cognition, 34*(3), 323-336.

Meador-Woodruff J. (1998) Dopamine Receptor Transcript Localization in the Human Brain. In: *Psychopharmacology: The Fourth Generation of Progress* (ed. W. SJ), Vol. 26, CD-ROM edn. Lippincott-Raven Publishers, Philadelphia.

Nieoullon A. (2002) Dopamine and the regulation of cognition and attention. *Prog Neurobiol*. 67, 53-83.

Pezawas, L., Verchinski, B. A., Mattay, V. S., Callicott, J. H., Kolachana, B. S., Straub, R. E., et al. (2004). The Brain-Derived Neurotrophic Factor val66met Polymorphism and Variation in Human Cortical Morphology. *Journal of Neuroscience, 24*(45), 10099-10102.

Prado, E., & Ullman, M. T. (Under Review). Can imageability help us draw the line between storage and composition? *Journal of Experimental Psychology: Language, Memory, and Cognition*.

Schultz W. (2001) Reward signaling by dopamine neurons. *Neuroscientist*. 7, p293-302.

Szeszko, P. R., Lipsky, R., Mentschel, C., Robinson, D., Gunduz-Bruce, H., Sevy, S., et al. (2005). Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Molecular Psychiatry, 10*, 631-636.

Trahan, D. E., & Quintana, J. W. (1990). Analysis of gender effects upon verbal and visual memory performance in adults. *Archives of Clinical Neuropsychology, 5*, 325-334.

Ullman, M. T. (2001). A neurocognitive perspective on language: The declarative/procedural model. *Nature Reviews Neuroscience, 2*, 717-726.

Ullman, M. T. (2004). Contributions of memory circuits to language: The declarative/procedural model. *Cognition, 92*(1-2), 231-270.

Ullman, M. T. (2007). The biocognition of the mental lexicon. In M. G. Gaskell (Ed.), *The Oxford Handbook of Psycholinguistics* (pp. 267-286). Oxford, UK: Oxford University Press.

Ullman, M. T. (In Press 2008). The role of memory systems in disorders of language. In B. Stemmer & H. A. Whitaker (Eds.), *Handbook of the Neuroscience of Language*. Oxford, UK: Elsevier Ltd.

Ullman, M. T., Maloof, C. J., Hartshorne, J. K., Estabrooke, I. V., Brovetto, C., & Walenski, M. (Under Revision). Sex, regularity, frequency and consistency: A study of factors predicting the storage of inflected forms.

Ullman, M. T., Miranda, R. A., & Travers, M. L. (2008). Sex differences in the neurocognition of language. In J. B. Becker, K. J. Berkley, N. Geary, E. Hampson, J. Herman & E. Young (Eds.), *Sex on the Brain: From Genes to Behavior* (pp. 291-309). NY NY: Oxford University Press.

Walenski, M., Mostofsky, S. H., & Ullman, M. T. (2007). Speeded processing of grammar and tool knowledge in Tourette's syndrome. *Neuropsychologia, 45*, 2447–2460.

Yebenes J. G. D. and Gomez M. A. M. (1993) Dopamine systems in the mammalian brain. In: *Parkinson's disease and movement disorders* (eds. J. Jankovic and E. Tolosa), 2 edn, pp. 14-34. Williams and Wilkins, London.