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Review

# Linking neurogenetics and individual differences in language learning: The dopamine hypothesis

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ABSTRACT

Fundamental advances in neuroscience have come from investigations into neuroplasticity and learning. These investigations often focus on identifying universal principles across different individuals of the same species. Increasingly, individual differences in learning success have also been observed, such that any seemingly universal principle might only be applicable to a certain extent within a particular learner. One potential source of this variation is individuals' genetic differences. Adult language learning provides a unique opportunity for understanding individual differences and genetic bases of neuroplasticity because of the large individual differences in learning success that have already been documented, and because of the body of empirical work connecting language learning and neurocognition. In this article, we review the literature on the genetic bases of neurocognition, especially studies examining polymorphisms of dopamine (DA)-related genes and procedural learning. This review leads us to hypothesize that there may be an association between DA-related genetic variation and language learning differences. If this hypothesis is supported by future empirical findings we suggest that it may point to neurogenetic markers that allow for language learning to be personalized.



## 1. Introduction

Research on the neuroscience of learning has been dominated by investigations of neuroplasticity that consider questions such as what aspects of the brain can change, under what conditions can they change, and at what age is change still be possible (e.g., Hubel and Wiesel, 1970; Merzenich et al., 1984; Recanzone et al., 1992). This research has informed our most fundamental understanding of learning and the brain. Increasingly, researchers are now paying close attention to the fact that large individual differences also exist in learning (e.g., Golestani and Zatorre, 2009; Wong et al., 2007). Therefore it is crucial that research on the neuroscience of learning should begin to examine the origins of these individual differences, including neurogenetic contributions. In this article, we will focus on a type of learning that shows large individual differences especially when learning begins in adulthood, namely language learning (e.g., Donyei, 2005;

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Johnson and Newport, 1989). Language is arguably a defining characteristic of humans (e.g., Donald, 1991; Jerison, 1973; Lewin, 1993), and its relationship with the brain has been extensively studied (e.g., Friederici et al., 2002; Hickok and Poeppel, 2007; Ullman, 2004). Language learning is therefore ideally suited for examining the biological bases of individual differences in learning. We will focus on the learning of grammar, an aspect of language that has been shown to be very difficult to acquire to native-like proficiency (Abrahamsson and Hyltenstam, 2009; Weber-Fox and Neville, 1996) and that has a relatively clear neurophysiological basis.

Numerous factors have been found to relate to success in language learning, including environmental and neural factors such as musical experience (Wong & Perrachione, 2007; Slevc and Miyake, 2006), the type of training (Morgan-Short et al., 2010, 2012; Norris and Ortega, 2000; Peach and Wong, 2004), working memory (Miyake and Friedman, 1998), and neuroanatomy (e.g., Golestani et al., 2007 Wong et al., 2008; Warrier et al., 2009). Although these studies have identified some sources of variability in language learning success, none have focused on genetics. The complexity of both language and the genome makes it challenging to identify specific genes that contribute to language learning, especially genes related to our focus of normal variation in learning (see gene *ASPM* for the perception of lexical tone, Wong et al., in press; see genes *ROBO1*, Hannula-Jouppi et al., 2005; *FOXP2*, Lai et al., 2003; *CNTNAP2*, Whitehouse et al., 2011 for work on communicative impairments and developmental delay). Fortunately, several characteristics of the dopaminergic system have been established, including relevant genes, brain systems, domain-general (e.g., cognitive) functions, and language functions. These characteristics can form the basis for developing informed hypotheses concerning the genetic basis of grammar learning. For example, studies have attributed grammar learning (and non-linguistic rule learning) to domain-general functions such as the procedural (implicit) memory system (e.g., Ullman, 2004), as well as to brain systems such as structures within the frontostriatal pathway (especially Broca's area) (e.g., Opitz and Friederici, 2003).

The dopaminergic system is tied to the frontostriatal pathway, among other brain structures (see Seamans and Yang, 2004 for a review), as well as to the procedural memory system (e.g., Shohamy and Adcock, 2010). In non-linguistic domains, the genes that encode dopamine (DA) receptors and transporters/catabolizers are tied to various types of procedural (rule) learning and brain responses (e.g., Karabanov et al., 2010). Based on the aforementioned facts about the dopaminergic system, we hypothesize that DA-related genes (and their interactions) may be associated with variation in grammar learning and functions of the frontostriatal pathway. This review provides our analysis and synthesis of the literature that led us to develop the above-stated hypothesis. It is our aim that this review and hypothesis will serve as a catalyst in generating new empirical research on the genetic bases of language learning.

Below, we will first discuss some basic facts about the DA system and its functions as they relate to procedural rule learning, reward, and cognition more broadly. We will specifically include studies that examine polymorphisms of DA-related genes and differences in performance on cognitive tasks. We will then focus the discussion on grammar learning, including the associated cognitive functions and brain systems. The relations among DA-related genes, procedural learning, grammar learning, and brain systems ultimately lead us to hypothesize that there may be a relationship between DA-genes and grammar learning.

## 2. The dopaminergic system and DA-related genes

Major divisions of the dopaminergic system contain neurons from the substantia nigra pars compacta and ventral tegmental area projecting to divisions of the striatum, cingulate cortex, amygdala, hippocampus, prefrontal cortex (PFC), and other regions (see Seamans and Yang, 2004 for a review). Once released presynaptically, DA interacts with one of five DA receptors D1, D2, D3, D4, and D5, encoded by genes *DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5* respectively. DA receptors are G protein-coupled receptors and are divided into two major classes: D1-like (D1 and D5) and D2-like (D2, D3 and D4). These receptors are distributed across regions of the central nervous system with different relative density levels. While very high densities of both classes of DA receptors are found in the striatum (across the caudate, putamen, and nucleus accumbens), a high density of D1, but not D2, receptors can be found in the frontal cortex (Camps et al., 1990; Khan et al., 2000; Little et al., 1995). In addition to interacting with DA receptors, once released, DA is eliminated extracellularly by the DA transporter (DAT) (encoded by gene *DAT1*) and the catabolizer enzyme Catechol-*O*-methyltransferase (COMT) (encoded by gene *COMT* ), primarily in the striatum and frontal cortex, respectively (e.g., Cass and Gerhardt, 1995; Cragg et al., 1997; Sesack et al., 1998; Wayment et al., 2001). Thus, levels of DAT and COMT ultimately affect the impact of DA. DA and DA receptors modulate a number of different molecular and cellular processes, including (2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid) (AMPA), N-methyl d-aspartate (NMDA), and $\gamma$-Aminobutyric acid (GABA) responses, which can lead to short- and long-term synaptic changes across different regions of the brain (see Seamans and Yang, 2004 for a review). One of these processes involves the DA-and-cAMP-regulated neuronal phosphoprotein (32 kDa) (encoded by gene *DARPP-32, also known as PPP1R1B*), which is found in the striatum (Ouimet et al., 1992) and affects functions and plasticity of DA receptors (e.g., Calabresi et al., 2000; Stipanovich et al., 2008). Over- and under-activation of DA receptors can lead to enhanced and/or impaired brain functions (e.g., Vijayraghavan et al., 2007; Zahrt et al., 1997).

It is worth noting that although our fundamental understanding of the dopaminergic system comes from animal research, and although substantial similarities exist between the non-human mammalian (especially primate) and human systems, there remain differences between the two systems. For example, a high density of D2 receptors can be found in the human hippocampal CA1/2 region but not in the monkey (Camps et al., 1990; Jiao et al., 2003; see Shohamy and Adcock, 2010 for a review). Therefore, when human functions (e.g., language) are examined, it is important to directly examine the human DA system. In our discussion below, we will focus on the human literature.

Different alleles of DA-related genes are consequential to the impact of DA on neurons. For the receptor genes, specific alleles have been linked to an increase/decrease of receptor binding. For example, the A1 allele of *DRD2* Taq1A is tied to reduced D2 receptor binding in the striatum (Noble, 2003). For the transporter genes, specific alleles are related to different levels of expression of the genes so that DA clearance rates could be affected. For example, Heinz et al. (2000) found individuals with the 9-repeat (at 3′-UTR region) allele had up to a 22% reduction in DAT protein compared to those with the 10-repeat allele, potentially making more DA available for individuals with the 9-repeat allele. As reviewed below, polymorphisms of DA-related genes can lead to differences in a variety of brain functions in humans, including psychiatric conditions, cognitive performance, and learning. Other genes are certainly relevant but we will only focus on those that have been examined in humans and whose functions we hypothesize to be linked to the kind of linguistic learning discussed in this article.

### 2.1. *Procedural learning and the DA system*

Decades of research have linked the dopaminergic system to a variety of learning paradigms that have been termed stimulus-reward learning, prediction error, reward learning, probabilistic (category) learning, reinforcement learning (learning the underlying rule of reinforcement), and trial-by-trial feedback learning (e.g., Frank et al., 2009; Karabanov et al., 2010; Klein et al., 2007). Both animal and human subjects have been included in this research, and many reviews have been published summarizing this line of work (e.g., Seamans and Yang, 2004; Shohamy and Adcock, 2010). There are inconsistencies in how learning paradigms are named across studies, and sometimes similar features are present in what are described as different learning paradigms. Nonetheless, a common feature of the different learning paradigms is *procedural learning*.

Procedural learning is a type of learning that is generally viewed as distinct from declarative learning. Declarative memory and learning is the knowledge that we have about facts and events related to our world. It is typically characterized as "knowledge that", encompasses representations of both semantic and episodic memory, and is primarily subserved by the medial temporal lobe, particularly the hippocampus, as well as by temporal and parietal cortical areas and BA 45/47 (Eichenbaum and Cohen, 2001; Squire and Knowlton, 2000; Ullman, 2001, 2004). Procedural memory and learning, which is often described as "knowledge how", underlies not only our ability to learn and perform skills and habits, such as typing, driving a car, throwing a ball, etc (Eichenbaum and Cohen, 2001), but also our ability to learn abstract rules. The procedural memory system is primarily associated with frontal/basal ganglia circuits and the inferior frontal gyrus (IFG), including BA44 (Ullman, 2001, 2004), and the PFC (e.g., Frank et al., 2004), where DA-associated neurons are found. Several cognitive tasks demonstrate procedural learning's relationship with the DA system. One such task is the "weather prediction" task (Gluck and Bower, 1988), in which subjects learn to predict category outcomes ("rain" or "sunshine") by the probabilistic linkage of a set of cards and these two categories. Knowlton et al. (1996) found that subjects with basal ganglia lesions have difficulty with such tasks. Another example of a procedural learning task is the learning of an artificial grammar. de Vries et al. (2010) found in healthy adults that performance in artificial grammar learning was improved after levodopa (a precursor of DA) intake. In our own work, we found that procedural memory is correlated with the learning of an artificial grammar, specifically, the learning of word and sound pattern combination rules (morpho-phonological grammar) (Ettlinger et al., 2009) and the learning of rules about how words are combined to form sentences (syntax) (Morgan-Short et al., submitted for publication). Moreover, such learning is associated with activation in PFC (including Broca's area) and basal ganglia (especially the striatum) (Ettlinger et al., 2010). Although it is often the case that procedural learning paradigms include learning via feedback in order for learners to learn the underlying pattern (e.g., Frank et al., 2004; Schultz et al., 1997), learning from trial-by-trial feedback is not always necessary to achieve procedural (more specifically probabilistic) learning. In their recent study, Li et al. (2011) found that both explicit instruction without trial-by-trial feedback and trial-by-trial feedback without explicit instruction resulted in successful probabilistic learning and activation in the striatum and PFC, though to different degrees.

### 2.2. *Procedural learning, DA receptors, and genes*

Research into the relationship between procedural memory/learning and the dopaminergic system has examined receptor binding and polymorphisms of DA-related genes more directly. In two Positron Emission Tomography (PET) studies, D2 receptor binding and receptor density have been found to be associated with (non-episodic) category fluency (Cervenka et al., 2008) and implicit sequence learning (Karabanov et al., 2010). In addition, Takahashi et al. (2010) found that healthy adults with lower striatal D1 receptor density show over- and under-estimations of low and high probabilities, respectively, in a version of the probabilistic category learning task. As discussed earlier, functions of DA-related genes, *DRD1-5*, *DAT1*, *COMT* and *DARPP-32*, can significantly affect DA's impact. Polymorphisms of these genes change gene products' biochemical properties and expression distribution. Therefore, it is not surprising that individuals with different genetic profiles may have different learning capabilities. For example, Jocham et al. (2009) and Klein et al. (2007) found that subjects with the *DRD2* (Taq1A) A1 allele show impaired probabilistic learning (including reversal learning). A1 allele is known to be associated with reduction in DA receptor D2 expression in the human frontostriatal pathway (Ritchie and Noble, 2003). In terms of reward and feedback learning, Krugel et al. (2009), Camara et al. (2010), Yacubian et al. (2007), and Dreher et al. (2009) have found an association between the *COMT* gene and the learning of reward structures and rapid adaptation to reward contingencies. More interestingly, Yacubian et al. and Dreher et al. found an important DA gene–gene interaction between the *COMT* and *DAT1*. Subjects with the lowest DA clearance rate, i.e., the combination of *COMT* Val158Met and *DAT1* 9-repeat genotype, showed the highest activity in the striatum and/or PFC activities associated with reward learning.

The fact that these two DA-related genes interact speaks to the importance of considering more than one DA gene within a single study. For example, reduced D2 receptor binding (*DRD2* TaqA1 allele) could be offset by a decrease in extracellular DA transport (*DAT1* 9-repeat). In addition to *COMT*, Frank et al. (2007) and (2009) found *DRD2* (C957T) and *DARPP-32* to be associated with different aspects of reinforcement learning. Both *DRD2* (C957T) and *DARPP-32* have been found to express in the striatum (Hirvonen et al., 2005, 2004; Stipanovich et al., 2008). Although not typically a focus, *DRD4* has also been examined in the reward learning literature and has been found to be linked to reward magnitude and activation in the anterior insula and cingulate cortex (Camara et al., 2010).

### 2.3. *Other cognitive functions*

In addition to procedural learning, DA and its related genes are associated with other cognitive functions such as working memory and attention. D1 receptor binding has not only been associated with working memory in animals (e.g., Williams and Goldman-Rakic, 1995), but also in humans (McNab et al., 2009). McNab et al. found that after 15 h of working memory training, adults not only improved on working memory capacity, but their D1 receptor binding potential was also changed. In addition to working memory, a study by Karlsson et al. (2009) also found D1 receptor binding to be related to inhibitory control. Unlike D1 receptors, which are more clearly linked to working memory and the PFC, the evidence for D2 receptors and working memory is mixed (Luciana et al., 1992; Muller et al., 1998). Furthermore, DA-related gene *COMT* has been found to be associated with working memory (Goldberg et al., 2003), executive function and inhibitory control (Savitz et al., 2006; Wilkosc et al., 2010 for a review), as well as attention deficits, which are associated with PFC deficits (Reuter et al., 2006). *DAT1* has been associated with performance gain in working memory training (Brehmer et al., 2009). Likewise, *DRD1, DRD2, DRD3,* and *DRD4* have been associated with executive control and inhibitory functions (Lane et al., 2008; Rodriguez-Jimenez et al., 2006; Rybakowski et al., 2005; Wilkosc et al., 2010). *DARPP-32* is associated with better performance in a battery of cognitive tasks, including intelligence quotient (IQ), working memory, and procedural learning (Meyer-Lindenberg et al., 2007). Taken together, these studies suggest that DA and related genes are associated with a broad array of human cognitive and learning functions that are associated with the PFC and the basal ganglia.

### 2.4. *Summary of DA-related genes, brain, and functions*

Although investigations into single nucleotide polymorphisms (SNP) and human behaviors have generated much attention, some results have failed to be replicated. Nonetheless, the majority of the DA-related genes we discussed here have been examined in multiple studies, some with converging multi-modal evidence. As far as these genes are concerned, we have every reason to believe that their associations with human cognitive functions are at least partially understood. Table 1 provides a summary of the DA-related genes that might be potentially relevant to language learning based on our literature review above. Subjects with the allele that results in increased impact of DA (what we marked "DA+") have been found to show better procedural learning, working memory, and/or executive function, with brain activity often seen in the striatum and different aspects of the PFC. It is worth noting that as in many genomic studies, opposite phenotypic effects of the same alleles or same effects of the alternate alleles have been observed for a variety of reasons such as culture-gene and gene–gene interactions (Battle et al., 2007; Chiao and Blizinsky, 2010; Kim et al., 2010). Alternatively, opposite phenotypic effects could be an indication of a Type-I error (false positive).

Although we focused on describing DA-related genes and their contribution to procedural learning, it is worth noting that functional impacts of these genes are also influenced by environmental factors such as psychosocial stressors (White et al., 2009) and smoking (e.g., Wiebe et al., 2009). However,

**Table 1 – Genes/SNPs that have been implicated in procedural learning and other cognitive functions, some of which may potentially be relevant to language learning. DA + allele = DA-preferential allele, , MeFC = Medial prefrontal cortex, OFC = Orbital frontal cortex.**

| Gene | Polymor-phism (dB SNP#) | DA + allele | Allele functions | Relevant brain regions | Relevant behavioral functions | Relevant studies |
|---|---|---|---|---|---|---|
| *DRD1* | A-48G (rs4532) | A | A allele increases DRD1 binding | PFC | Executive function, inhibitory control | Lane et al. (2008); Rybakowski et al. (2005) |
| *DRD2* | Taq1A (rs1800497) | A2 | A1 allele reduces DRD2 density and DA binding | MeFC, Striatum, OFC, Cingulate | Probabilistic Learning | Klein et al. (2007); Jocham et al. (2009) |
| *DRD2* | C957T (rs6277) | T | T allele increases DRD2 binding | Striatum | Reward Learning, executive functions | Rodriguez-Jimenez et al. (2006); Frank et al. (2009), (2007); Hirvonen et al. (2004); Hirvonen et al. (2005) |
| *DAT1* | (rs28363170) | 9-R ("S") | 9-R lowers DAT expression | PFC, OFC, striatum | Reward Learning | Rueda et al. (2005); Dreher et al. (2009) |
| *COMT* | Val158Met (rs4680) | Met | Met allele decreases COMT enzymatic activity | PFC, OFC, striatum | Reward Learning, executive function | Frank et al. (2009); Yacubian et al. (2007); Dreher et al. (2009) |

as far as we are aware, the gene–environment interaction studies conducted so far have yet to examine how such interaction might affect language learning.

## 3. Language learning and memory systems

Thus far, we have discussed different aspects of the dopaminergic system, including genomic studies, and how it relates to procedural learning and other aspects of cognition including working memory and inhibitory control. Here, we discuss more specifically how language learning might be related to the dopaminergic system. These studies all point to successful grammar learning being tied to procedural memory and its associated brain structures. Furthermore, working memory may also be relevant.

### 3.1. *Theoretical models*

After many years of learning, many adults still have difficulty mastering a foreign language/second language (L2). While the learning of certain aspects of foreign languages, such as vocabulary, can be acquired with nearly native-like proficiency by many adult learners (Weber-Fox and Neville, 1996), rules governing combinations of linguistic elements (grammar) are relatively difficult to acquire (Abrahamsson and Hyltenstam, 2009; Johnson and Newport, 1989; Weber-Fox and Neville, 1996). These grammatical rules include rules governing how sound elements or phonemes are combined (phonology), how words are created (morphology), and how words and their derivations are combined to form sentences (syntax). Research studies have provided evidence that the learning of vocabulary (lexicon) and grammar is tied to the declarative (explicit) (Damasio et al., 1996) and procedural (implicit) (Altmann, 2002; Gupta and Dell, 1999; Marslen-Wilson and Tyler, 2007) memory systems, respectively (Ullman, 2001, 2004). The connection between the lexicon and declarative memory and between grammar and procedural memory is framed explicitly under the Declarative/Procedural (DP) model (Ullman, 2001, 2004) and other similar models (Marslen-Wilson and Tyler, 1997; Paradis, 1994) (see Table 2 for a summary). According to this model, for the native/first language (L1), the mental lexicon (vocabulary) is expected to rely on declarative memory, while the mental grammar is expected to rely on procedural memory (Ullman, 2001, 2004). Evidence implicating the importance of grammar and procedural memory in L1 acquisition comes from work in children with specific language impairment (SLI), a developmental language impairment that can often involve deficits in grammar usage (e.g., Rice and Oetting, 1993; Rice et al., 2009). Specifically, Evans et al. (2009) found that SLI children were also impaired in statistical learning, a type of learning that is viewed as implicit. If it is in fact the case that language (grammatical) impairment in childhood is linked to the procedural system, our DA-related gene-grammar linkage hypothesis might also apply to L1 acquisition and impairment. Furthermore, DA-related genes might interact with other genes that have been implicated in SLI, including Contactin-associated protein-like 2 (*CNTNAP2*) (Vernes et al., 2008), ATPase, Ca++ transporting, type 2C, member 2 (*ATP2C2*), and c-maf-inducing protein (*CMIP*) (Newbury et al., 2009).

Although some variation is expected in L1 acquisition, substantially more is expected in L2 acquisition in adulthood. The relationship between the memory systems and mental lexicon and grammar is arguably more complex for L2 acquisition (Ullman, 2001, 2005). On one hand, as in the L1, declarative memory is expected to underlie the lexicon in L2 at all levels of proficiency and experience with the L2. On the other hand, L2 grammar, unlike L1 grammar, is expected to be dependent on declarative memory at lower levels of proficiency and experience, but may come to rely on procedural memory at higher levels of L2 proficiency and experience. In fact, it may be the case that one must come to rely on procedural memory for grammatical processing in order to reach the highest levels of L2 proficiency. Thus, from the standpoint of individual differences and cognitive indicators of learning success, L2 learners who reach higher levels of proficiency in an L2 may be the individuals that possess a better procedural learning ability. Evidence for the DP (and other similar) models includes behavioral (psycholinguistic) (Bowden et al., 2010; Neubauer and Clahsen, 2009; Silva and Clahsen, 2008) and neuroimaging studies of L1 and L2 learners (e.g., Golestani and Zatorre, 2004; Xue et al., 2004). For example, neuroimaging studies suggest that lexical processing in L1 and L2 relies on similar neural substrates (Chee et al., 1999; Klein et al., 1999; Xue et al., 2004), but that the neural substrates underlying L1 and L2 grammatical processing differ either qualitatively or

**Table 2 – Primary characteristics of the declarative and procedural memory systems and functions in first and second languages, based on Ullman (2001, 2004), Ullman et al. (2005).**

| | Declarative memory | Procedural memory |
|---|---|---|
| Neural basis | • Medial temporal lobe, particularly the hippocampus<br>• Neocortical regions, including temporal and parietal cortex and BA 45/47 | • Frontal/basal ganglia circuits<br>• IFG, particularly BA 44 |
| Non-linguistic function | • Semantic (facts) and episodic (events) memory | • Motor and cognitive skills and habits |
| Primary linguistic function for L1 | • L1 lexicon | • L1 grammar |
| Primary linguistic function for L2 | • L2 lexicon and grammar at *low* proficiency and exposure<br>• L2 lexicon at *high* proficiency and exposure | • No posited role for L2 lexicon or grammar at *low* proficiency and exposure<br>• L2 grammar at *high* proficiency and exposure |

*Note.* BA = Brodmann area.

quantitatively, with the area and level of activation becoming more L1-like (Golestani and Zatorre, 2004; Perani et al., 1998) and more specific to IFG (Abutalebi, 2008) at higher levels of proficiency.

It is worth noting that alternative models such as the Convergence Hypothesis (Green, 2003) and the Competition Model (Hernandez et al., 2005) exist to make predictions about L2 learning. However, the most important aspect of our discussion here pertains to the dopaminergic system which overlaps with the procedural memory system. These alternative models do not make explicit predictions regarding the role of the dopaminergic system in language learning, do not explain why procedural memory is often tied to grammar learning, and most importantly do not reject the notion of the dopaminergic system being intimately linked to grammar learning.

Besides procedural memory, working memory has also been found to be associated with L2 learning, presumably because it facilitates grammar and other kinds of learning by allowing relevant information to be kept active (Mackey et al., 2010; see Miyake and Friedman, 1998 for a review of classical studies). Aspects of working memory have been attributed to the PFC, where DA-related genes (especially *DRD1* and *COMT*) are expressed. Thus, by examining these genes, it is also possible to examine the potential contribution of working memory in L2 learning.

### 3.2. *Procedural system and artificial grammar learning*

The aforementioned studies mostly concern L2 learning in the classroom or other "naturalistic" learning environments. However, much research has examined artificial grammar learning in the laboratory. Clearly, the potential limitation of artificial language paradigms is their ecological validity. However, because of the challenge of establishing internal validity in natural language studies, the best method for investigating certain language-related issues may be studies that consider converging evidence from artificial and natural language studies. It is worth mentioning that in our own study designed to explicitly compare artificial grammar learning in the laboratory and L2 learning in the classroom, we found a close connection between the two (Ettlinger et al., 2011).

In addition to studies on actual ("naturalistic") L2 learners (typically learners in the classroom), support for the DP model comes from the artificial grammar learning (short-term learning in the laboratory) literature. When presented with segmented words in a continuous speech stream, listeners can learn to rely on transitional probabilities of phonemes and syllables (e.g., Saffran et al., 1996), which have been found to be subserved by the PFC and basal ganglia, among other structures (McNealy et al., 2006). In addition to learning speech-sound transitional probabilities and word segmentation, language users need to learn how words are created. In the process of creating words, changes in sound structures may also take place. For example, English learners know that to create the plural forms of many nouns, the suffix/-s/is added at the end of a word (e.g., cat-s = cat + s). However, sometimes the/-s/has to be altered because of its surrounding phonological context. For example, to signal the plural form of 'dog', the/-s/is changed to a/-z/sound in spoken language (dogz) because the final sound/g/in 'dog' is articulatorily more similar to a/z/sound than an/s/. In a series of recent studies, we have found that the learning of some morpho-phonological rules in an artificial grammar is associated with procedural memory (Ettlinger et al., 2009) and the fronto-striatal pathway (Ettlinger et al., 2009). Perhaps the most frequently cited example of artificial grammar learning is the learning of syntax. For example, Opitz and Friederici (2003) found increasing levels of activation in Broca's area during the learning of phrase structure rules via the artificial language BROCANTO. Using a modified version of this language, BROCANTO2, Morgan-Short et al. (2012) found a reliance on lexical/semantic processing for a syntactic structure (phrase structure) at low proficiency but native-like processing of the same structure at high levels of proficiency, supporting the DP model for a group of learners that received implicit training, i.e., exposure to the language without provision of grammatical explanation. Because artificial languages have been well documented in the literature as a source for insights into grammar learning, they can be used as starting points for investigations into the polymorphisms of DA-related genes and language learning. Although the question of interest here is DA-related genes and grammar learning, more direct evidence for the involvement of the DA system in grammar learning would involve direct targeted manipulation of the availability and impact of DA, as in pharmacological studies (e.g., de Vries et al., 2010).

### 3.3. *Counter-evidence and other challenges*

We have discussed our hypothesized framework for understanding the neurogenetics of language learning by highlighting the relationships between genes and specific brain systems, and by describing how these brain systems control the domain-general cognitive functions that appear to be integral to language learning. However, we should note some important caveats. First, much of the evidence we have discussed on the relationships among the brain, domain-general cognitive processing, and language come from studies of native language ability. These relationships are less clear with respect to L2 learning. On the one hand, Abutalebi (2008) highlights evidence suggesting that L2 learning depends on the same sets of neural processes as L1 learning. Ullman et al. (2005), however, suggests that L2 learning makes far greater use of the declarative memory system and corresponding neural substrates, namely the medial temporal lobe, at least during initial stages of learning.

Furthermore, the dissociation between procedural memory brain regions and declarative memory brain regions has been called into question by recent research. For example, Shohamy et al. (2009) and Newell et al. (2007) have found evidence that medial temporal regions play an important role in probabilistic learning. This may not be surprising given that dopamine receptors can be found in structures such as the hippocampus (see Shohamy and Adcock, 2010 for a review), and hippocampal structures are strongly associated with declarative memory (e.g., Squire and Knowlton, 2000).

Also, in a recent morpho-phonological grammar learning study, Ettlinger et al. (2009) found that procedural memory is most intimately involved in the learning of simple

concatenation rules, but that acquiring a grammar based on analogy depends on declarative memory. Thus, it is important to note that although we hypothesize that there may be a relationship among procedural memory, DA, and grammar learning, the hypothesis may only speak to some aspects of grammar learning. Our goal in this review article is to posit potential links between grammar learning and certain DA-related genes in order to encourage future investigations that consider the specific types of grammar learning that we hypothesize to be tied to DA-related genes.

The impact of DA on our nervous system and neurocognitive functions is obviously extremely broad, and its effects reach far beyond language learning. The question of whether certain types of grammar learning are also associated with subtle variations of some other DA-related behaviors would require future studies to determine.

## 4. Other considerations in studying the neurogenetics of language learning

### 4.1. *Other relevant genes*

Although this review primarily concerns the dopaminergic system and its relationship with normal variation of language learning, genes that have been implicated in communication disorders are undoubtedly relevant (see Newbury and Monaco, 2010 for a recent review). We will discuss several key areas of findings here. SLI has been linked to chromosome 16q and 19q (Bishop, 2001; Rice, 2007; SLI Consortium, 2004). More recently, several genes, such as *CNTNAP2* (Vernes et al., 2008), and *ATP2C2* and *CMIP* (Newbury et al., 2009), have been found to be associated with SLI. In developmental dyslexia, a disorder related to language, Roundabout homolog 1 (*ROBO1*) (Hannula-Jouppi et al., 2005) and *KIAA0319* (Cope et al., 2005) have been implicated.

A number of studies have examined the genetic basis of stuttering (fluency disorders). One twin study involving over 4000 twins showed that genetic factors might explain a majority of the variance in stuttering (Gerber, 2001) and subsequent studies have linked this disorder to a number of chromosomes (e.g., 1q and 7q, Riaz et al., 2005). More recently, mutations of several genes have been proposed to play a role in a subset of cases of stuttering, including N-acetylglucosamine-1-phosphotransferase, gamma subunit *(GNPTG)*, N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits (*GNTAB*), and N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase *(NAGPA)* (Kang et al., 2010).

Perhaps the most frequently discussed genetic deficit of human communication is one that affects the KE family in which 15 individuals show developmental speech and language impairments (Hurst et al., 1990; Vargha-Khadem et al., 1995; Gopnik, 1990). Their impairments have later been linked to the *FOXP2* (*SPCH1*) gene (Lai et al., 2001, 2000; Fisher et al., 1998), which is expressed in motor-related circuits, including the basal ganglia, thalamus, inferior olives, and cerebellum (Lai et al., 2003). *FOXP2* belongs to a member of the large FOX (Forkhead box) family of transcription factors. Mutations of *FOXP2* are associated with difficulties in the learning and production of coordinated sequences of orofacial movements (e.g., Vargha-Khadem et al., 2005; Shriberg et al., 2006). The involvement of *FOXP2* in speech production function is confirmed by structural and functional neuroimaging studies. Voxel-based morphometry (VBM) has shown significantly different amounts of gray matter in motor-related areas in affected members of KE family compared to unaffected members (Watkins et al., 2002), which corroborates with a PET study showing anomalies in activation in the motor-related areas (Vargha-Khadem et al., 1998). An functional Magnetic Resonance Imaging (fMRI) study comparing affected and unaffected members of the KE family in covert and overt verb generation tasks revealed that while the unaffected members showed a typical left-dominant distribution of activation including Broca's area, the affected members showed more posterior and bilateral patterns (Liegeois et al., 2003; see Vargha-Khadem et al. (2005) and Fisher and Scharff (2009) for reviews of these neural findings related to *FOXP2*). Similarly, Pinel et al. (2012) found common polymorphisms of *FOXP2* to be associated with variation in activation of language-related brain areas, including Broca's area. More relevant to our hypothesis, Enard et al. (2009) further demonstrated in a mouse model that insertion of two human-specific amino acid substitutions into the mouse version of the *Foxp2* protein resulted in decreased DA concentrations in cortico-basal ganglia circuits, altered plasticity of those circuits, and subtle changes in pup vocalization. Thus, our hypothesized association between DA and grammar learning could also be related to *FOXP2*. Future studies should consider how genes related to communication disorders (including *FOXP2*) might be involved in the DA system, and how the DA-related genes we reviewed might interact with the genes to ultimately give rise to successful language learning and impairment.

### 4.2. *Developmental and environmental factors*

Although the scope of this review is restricted to the potential genetic contributions to language learning in adulthood, we must acknowledge that developmental and environmental factors contribute substantially to language learning in general. Language input is a strong predictor of measures of language development in children such as vocabulary size (Huttenlocher et al., 1991). Moreover, there is extensive evidence suggesting that by the end of the first year, infants' sensitivity to speech sounds reduces from both native and non-native sounds to only sounds that occur in their native language (e.g., Werker, 1984; Werker and Tees, 1984; Polka and Werker, 1994), presumably due to the degree of exposure to their native language. Interestingly, with training, adults are able to learn foreign speech sounds (e.g., Pisoni et al., 1982; Jamieson and Morosan, 1989; Lively et al., 1993; Bradlow et al., 1997) albeit with great difficulty. As we discussed above, there is also a large degree of variability in how successfully adults learn new speech sounds (e.g., Wong et al., 2007) and grammar (Ettlinger et al., 2009).

Most interestingly, different training paradigms may result in variable degrees of success, depending on the learner (Perrachione et al., 2011), suggesting that environment (training in this case) plays an important role in influencing how learning success. In this Perrachione et al. study, English-

speaking subjects learned a speech contrast that occurs in Mandarin Chinese but not English. Learners who showed poorer pre-training auditory perception were most affected by the type of training they received. Specifically, training that introduced trial-by-trial variability in the training stimuli substantially impaired these learners, whereas learners who showed stronger auditory perceptual ability benefited more from trial-by-trial variability in training. These results suggest that it might be possible to personalize training for individual learners. Although, the evidence here is from using a behavioral measure (i.e., auditory perceptual ability) for personalizing learning, it is conceivable that genomic information can be used in the future.

### 4.3. *Genome-wide association studies (GWAS) and whole genome sequencing (WGS)*

In considering future research on the neurogenetics of language learning, it is important to consider newer technological advances. WGS and GWAS have become the norm for many studies of complex traits and have provided information about the molecular genetics of a number common diseases (e.g., McCarthy et al., 2008; Lyssenko et al., 2008; Lupski et al., 2010). Because of the substantial cost associated with performing a GWAS, which require a very large sample and often a replication sample, we believe it would be more cost effective to perform some initial hypothesis-driven experiments with a set of candidate genes (e.g., DA-related genes) for understanding language learning. These initial experiments not only allow for a demonstration that it is possible to examine the genetic bases of language learning, it can also inform us about the underlying molecular neurobiological mechanisms. If our hypothesis about DA-related genes and language learning is correct, a GWAS and/or WGS study can be informative beyond listing SNPs that show statistical significance. For example, GWAS can contribute to an understanding of potential gene–gene interactions that give rise to the impact of DA, and potentially other non-DA related neural pathways that are relevant to language learning for further hypothesis-driven experiments.

## 5. Conclusion

Independent lines of research have focused on the DA system and procedural learning on one hand, and language learning and cognitive and brain systems on the other. In this article, we argue that in fact these two lines of research should be considered in tandem in order to gain insight into the neurogenetics of language learning. Future research should begin to examine how genetic polymorphisms that have been linked to procedural learning might also be linked to language learning. With this linkage information, future research can then examine whether learners with different genotypic profiles can benefit from different kinds of training. The latter effort will be among the first to extend the concept of personalized medicine from pharmacogenetics (Eichelbaum et al., 2006; Evans and Johnson, 2001) to human learning. If successful, such a "personalized learning" approach will not only be useful for language learning, but many forms of skill learning that are relevant to neuropsychological and communication disorders, as well as physical and occupational medicine.

Although our focus was on the DA system and language learning, genes that are relevant to communication disorders are likely part of the genetic network that governs how language is learned as well. Future research is needed to examine the relative contributions of these genes and the type of language learning that they contribute.

Finally, it is important to note that the DA system also affords a very general impact on the nervous system beyond language learning and processing. Thus, future research should consider the degree to which the polymorphisms of the genes we discussed impact language and other cognitive capabilities in order to delineate their domain-specific and domain-general effects.

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