Neuropsychologia 67 (2015) 121–131

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Dopamine receptor D4 (DRD4) gene modulates the influence of informational masking on speech recognition

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ARTICLE INFO

Article history:
Received 25 July 2014
Received in revised form
9 December 2014
Accepted 10 December 2014
Available online 11 December 2014

Keywords:
Speech perception
Individual difference
Informational masking
Executive attention/working memory capacity
DRD4

ABSTRACT

Listeners vary substantially in their ability to recognize speech in noisy environments. Here we examined the role of genetic variation on individual differences in speech recognition in various noise backgrounds. Background noise typically varies in the levels of energetic masking (EM) and informational masking (IM) imposed on target speech. Relative to EM, release from IM is hypothesized to place greater demand on executive function to selectively attend to target speech while ignoring competing noises. Recent evidence suggests that the long allele variant in exon III of the *DRD4* gene, primarily expressed in the prefrontal cortex, may be associated with enhanced selective attention to goal-relevant high-priority information even in the face of interference. We investigated the extent to which this polymorphism is associated with speech recognition in IM and EM conditions. In an unscreened adult sample (Experiment 1) and a larger screened replication sample (Experiment 2), we demonstrate that individuals with the *DRD4* long variant show better recognition performance in noise conditions involving significant IM, but not in EM conditions. In Experiment 2, we also obtained neuropsychological measures to assess the underlying mechanisms. Mediation analysis revealed that this *listening condition-specific* advantage was mediated by enhanced executive attention/working memory capacity in individuals with the long allele variant. These findings suggest that *DRD4* may contribute specifically to individual differences in speech recognition ability in noise conditions that place demands on executive function.

1. Introduction

In typical social settings, speech perception often takes place in the presence of interfering background noise. Individual listeners vary substantially in their ability to perceive speech in noisy conditions (e.g., Gilbert et al., 2013; Song et al., 2011; Wightman et al., 2010; Wilson et al., 2007). For example, Gilbert et al. (2013) showed that the overall accuracy of sentence recognition in multi-talker babble ranged from approximately 40–76% in a group of 121 young, normal-hearing adults. Previous work has examined how sensory (e.g., subcortical representation of speech sounds Chandrasekaran et al., 2009; Parbery-Clark et al., 2011; Song et al., 2011) and cognitive factors (e.g., working memory, Anderson et al., 2013; Koelewijn et al., 2012; Zekveld et al., 2013) contribute to individual differences observed in speech recognition in noise tasks. A general source of individual difference is genetic variation (e.g., Bellgrove et al., 2005; Bouchard et al., 1990; Friedman et al., 2008). However, to our knowledge, no studies have examined the role of genetic factors in individual difference in speech perception in noise. To this end, the current study examined the effect of genetic variation on individual differences in executive function as it relates to speech recognition ability in challenging listening environments.

1.1. Energetic masking vs. informational masking and executive function

To recognize speech in noisy environments, one must overcome at least two types of interferences – energetic masking and informational masking (Brungart, 2001). Energetic masking (EM)

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http://dx.doi.org/10.1016/j.neuropsychologia.2014.12.013
0028-3932/

occurs when noises spectro-temporally overlap with portions of target speech signals in the auditory periphery, leading to a degraded neural representation of the signals (Arbogast et al., 2002; Brungart, 2001; Freyman et al., 2004; Freyman et al., 1999; Shinn-Cunningham, 2008). Informational masking (IM) interferes with target speech processing at more central levels of information processing. IM interference occurs even though the target signal and competing noises are relatively well represented in the auditory system (Arbogast et al., 2002; Freyman et al., 2004; Shinn-Cunningham, 2008). These central interferences include misattribution of components of the noise to the target (and vice versa), attentional distraction from the target, linguistic interference from the noise, and increased cognitive load (Cooke et al., 2008).

Previous work suggests that the mechanisms underlying EM and IM are at least partially dissociable. For example, Van Engen (2012) found that speech recognition performance in EM conditions did not predict performance in IM conditions. To cope with EM or IM, listeners are required to segregate the target source from the maskers (Shinn-Cunningham, 2008). Since the target speech and maskers are simultaneously represented in the brain (Sussman et al., 2014), to recognize target speech, listeners also need to exert top-down attention to select the target and inhibit/ignore the influences from the interfering noises (Shinn-Cunningham, 2008). As discussed before, relative to EM, IM causes more substantial central interferences, which are likely to interfere with top-down processes. Hence, relative to EM, release from IM likely places greater demands on executive functions such as selective attention, inhibitory control, and working memory to counteract central interferences. Indeed, existing studies have shown that that working memory capacity is associated with speech recognition performance in IM conditions (Koelewijn et al., 2012; Zekveld et al., 2013), but not in EM conditions (Besser et al., 2013; Koelewijn et al., 2012; Zekveld et al., 2012, 2013). These executive processes (selective attention, inhibition, and working memory) critically depend on prefrontal cortical function (Aben et al., 2012; Alvarez and Emory, 2006; Collette and Van der Linden, 2002; Faraco et al., 2011; Kane and Engle, 2002).

1.2. *Executive function, dopamine, and dopamine D4 receptor (DRD4) gene*

It is widely recognized that the neurotransmitter dopamine modulates frontostriatal circuitry critical to working memory and inhibitory control (for review, see Cools and D'Esposito, 2011; Seamans and Yang, 2004). Many studies have examined the relationship between prefrontal dopamine D1 and/or D2 receptors and prefrontal functions (e.g., Takahashi et al., 2008; Vijayraghavan et al., 2007). For example, Takahashi et al. (2008) demonstrated an inverted U-shape relation between D1 receptor expression in prefrontal cortex and executive function measured by Wisconsin Card Sorting Test. Some other studies have focused on the role of striatal dopamine in executive functions such as working memory and attention (e.g., Cools et al., 2008; Landau et al., 2009). For instance, Cools et al. (2008) showed that striatal dopamine synthesis capacity was positively correlated with working memory capacity as measured with listening span, with higher dopamine synthesis capacity in individuals with higher working memory capacity. Recently, there are considerable interests in understanding the role of dopamine-related genes in executive function (for review, see Barnes et al., 2011). For example, Li et al. (2013) demonstrated that the DARPP-32 gene, which is richly expressed in the striatum, modulated auditory selective attention in situations where listeners have to focus on goal-relevant information and ignore irrelevant information.

Another well-studied dopamine gene associated with executive function is the dopamine D4 receptor (*DRD4*) gene, which is located on chromosome 11p15.5 and encodes a post-synaptic D4 dopamine receptor. Unlike DARPP-32 gene, this gene is primarily expressed in the prefrontal cortex (Oak et al., 2000). A polymorphism of *DRD4* gene lies in the 48 base pair (bp) variable number of tandem repeats (VNTR) in exon III. This polymorphism alters the sensitivity of the D4 receptor through influencing the receptor protein length in the third cytoplasmic loop (Van Tol et al., 1992). The 48-bp sequence is repeated between 2 and 11 times (Van Tol et al., 1992). The number of repeats have been shown to associate with the potency of dopamine to inhibit cyclic adenosine monophosphate (cAMP) formation, with 7-repeat variant showing twofold reduction in the potency relative to 2- and 4-repeat (Asghari et al., 1995). Functionally, this polymorphism has been shown to associate with executive functions (e.g., Kegel and Bus, 2013), presumably via prefrontal activation (e.g., middle and inferior frontal gyrus) related to executive functions (Gilsbach et al., 2012).

In the literature, based on the repeat length, individuals have often been grouped as either "long" carriers (7 or more repeats) or "short" carriers (6 or fewer repeats). Interestingly, *DRD4* long carriers have demonstrated disrupted or enhanced executive attention (Gizer and Waldman, 2012; Kieling et al., 2006; Swanson et al., 2000), inhibitory control (Congdon et al., 2008; Krämer et al., 2009; Langley et al., 2004; Loo et al., 2008), and short-term memory or working memory (Altink et al., 2012; Boonstra et al., 2008; Loo et al., 2008). To date, it remains unclear what leads to the mixed evidence regarding the role of *DRD4* in modulating executive function. A recent study suggests that *DRD4* long carriers may show enhanced selective attention to goal-relevant high-priority information even in the face of interference, but may demonstrate impaired attention to goal-irrelevant low-priority information (Gorlick et al., 2014). Of relevance to our study, this study showed that *DRD4* long carriers demonstrate superior performance on the Operation Span Task. This task measures working memory as well as domain-general executive attention (Conway et al., 2005), which requires selective attention to update and maintain high-priority items in memory while also performing a distracting secondary task. As discussed before, these executive attentional processes contribute to the release from IM. Thus, we predict that *DRD4* long carriers will demonstrate better performance in speech perception in IM conditions, but not during EM conditions.

1.3. *Aims of current study*

We test this hypothesis by examining the impact of the *DRD4* polymorphism on speech perception under a variety of noise conditions. In a pilot experiment (Experiment 1), with a small adult sample that was not screened for neuropsychiatric disorders, we classified participants as *DRD4* long carriers (i.e. homozygous or heterozygous for an allele of 7 or more repeats) or as *DRD4* short homozygotes (i.e. both alleles <7 repeats). We compared their sentence recognition performance in 2-talker babble (IM) and pink noise (EM) across a range of signal-to-noise ratios (SNR: -4 to 20 dB). In Experiment 2, we aimed to replicate and extend the findings from Experiment 1 with a larger independent sample that was screened for neuropsychiatric disorders. We compared sentence recognition performance in *DRD4* long and short carriers across IM and EM conditions at a fixed SNR. Importantly, we also examined the extent to which the genetic influence on speech perception was mediated via executive function by administrating a battery of neuropsychological tests including measures on executive attention/working memory capacity. Consistent with a previous study demonstrating enhanced executive attentional processes in *DRD4* long carriers (Gorlick et al., 2014), we predict