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The Genetic contribution to solving the cocktail-party problem

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Article

The Genetic contribution to solving the cocktail-party problem

Cocktail-party listening

Residual (43%)

Genetic factors (57%)

Genetic correlation = 0.39

Residual (48%)

Genetic factors (52%)

Hearing thresholds
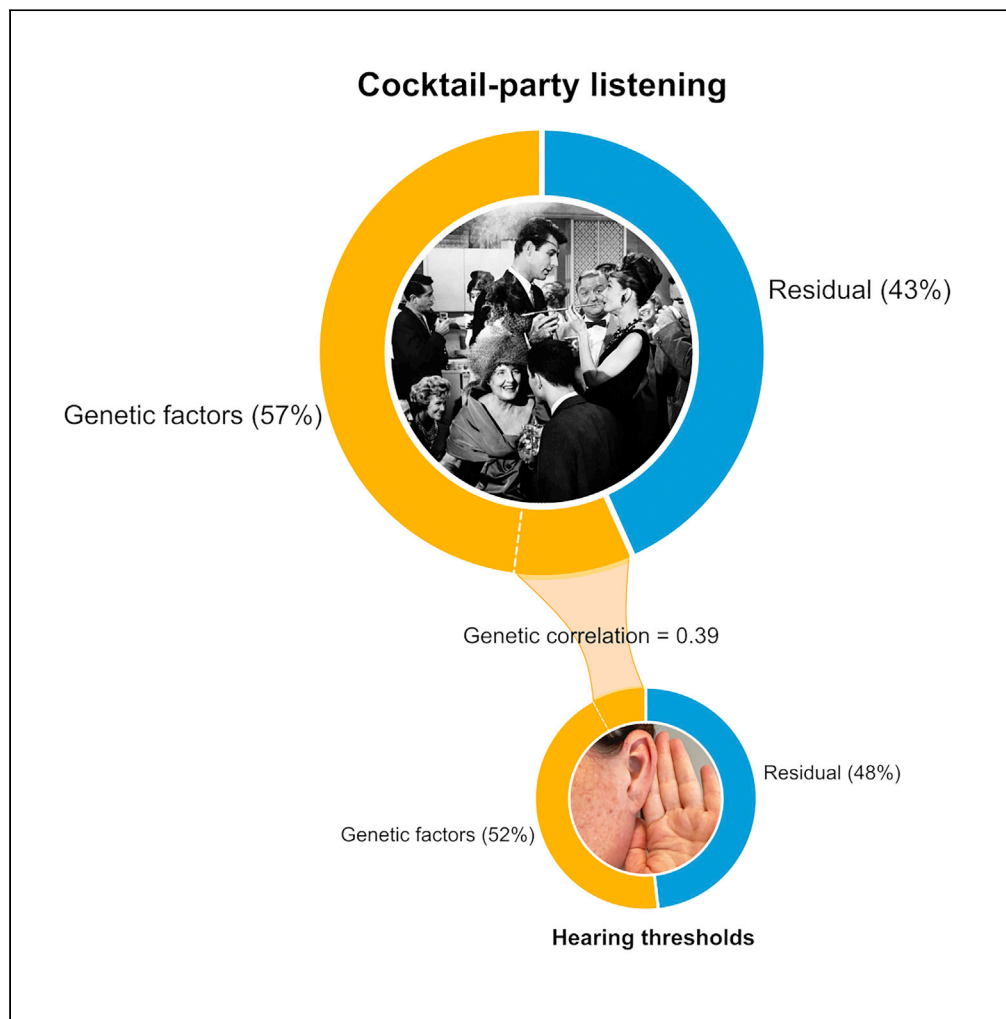
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Highlights

Humans show large variation in their abilities to solve the "cocktail-party problem."

Around half the variance in cocktail-party listening ability is explained by genes

There is moderate genetic correlation between this ability and hearing thresholds

Findings may represent a step toward identifying genes for "hidden hearing loss

iScience

Article

The Genetic contribution to solving the cocktail-party problem

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SUMMARY

Communicating in everyday situations requires solving the cocktail-party problem, or segregating the acoustic mixture into its constituent sounds and attending to those of most interest. Humans show dramatic variation in this ability, leading some to experience real-world problems irrespective of whether they meet criteria for clinical hearing loss. Here, we estimated the genetic contribution to cocktail-party listening by measuring speech-reception thresholds (SRTs) in 425 people from large families and ranging in age from 18 to 91 years. Roughly half the variance of SRTs was explained by genes ($h^2 = 0.567$). The genetic correlation between SRTs and hearing thresholds (HTs) was medium ($\rho_G = 0.392$), suggesting that the genetic factors influencing cocktail-party listening were partially distinct from those influencing sound sensitivity. Aging and socioeconomic status also strongly influenced SRTs. These findings may represent a first step toward identifying genes for "hidden hearing loss," or hearing problems in people with normal HTs.

INTRODUCTION

While the defining feature of clinical hearing loss is reduced sensitivity to sounds (Michels et al., 2019), detecting quiet sounds is not the main problem listeners experience in everyday situations. Rather, the commonest complaint is difficulty understanding or following audible sounds, particularly speech, in the presence of irrelevant background sounds (Gatehouse and Noble, 2004). This is known as the cocktail-party problem (Cherry, 1953; reviewed by Bee and Micheyl, 2008; Bronkhorst, 2015). Listeners with ostensibly normal hearing—that is, hearing thresholds (HTs) within the clinically normal range—show large individual differences in performance on laboratory tasks involving cocktail-party listening (e.g., Ruggles et al., 2011). Furthermore, in the real world, a significant proportion of people who report problems with their hearing do not meet the criteria for hearing loss (e.g., Davis, 1989; Hind et al., 2011; Tremblay et al., 2015). It remains unclear why cocktail-party listening shows large individual differences and why some people experience hearing problems despite having normal HTs. Conventional wisdom says that they are caused by some combination of genetic and environmental factors, although the specific factors and their relative strengths are not well understood.

There are many genetic forms of hearing loss (for a complete list, see Van Camp and Smith, n.d.). By definition, these are caused by specific mutations that can be identified within affected individuals via genotyping arrays or sequencing (e.g., Sloan-Heggen and Smith, 2016). Most genetic forms of hearing loss are prelingual (Shearer et al., 2017). They are also rare, affecting two or three out of every 1,000 children (Vohr, 2003). By contrast, age-related sensorineural hearing loss (ARSHL) is extremely common, affecting around 40% of adults over 60 years old (Hoffman et al., 2017). Our understanding of the genetics of ARSHL lags behind that of prelingual hearing loss (Wells et al., 2020). Prior family studies have shown that HTs are heritable, or correlated among biological relatives, suggesting that there is a sizable genetic component to ARSHL (Duan et al., 2019; Hendrickx et al., 2013; Kvestad et al., 2012; Raynor et al., 2009). Furthermore, genome-wide association studies (GWAS) have implicated on the order of 100 genomic risk loci for ARSHL (Fransen et al., 2015; Girotto et al., 2011; Hoffmann et al., 2016; Ivarsdottir et al., 2021; Nagtegaal et al., 2019; Van Laer et al., 2010; Vuckovic et al., 2015; Wells et al., 2019). However, GWAS loci explain a small fraction of the overall variance of ARSHL, both individually and collectively, demonstrating that

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ARSHL is polygenic (although rare genetic variation may confer larger effects in extreme cases; cf. Boucher et al., 2020).

While reduced sound sensitivity is the primary limiter of speech intelligibility, especially in older listeners (Humes et al., 2020; Humes and Dubno, 2010), successful cocktail-party listening requires more than just correctly identifying phonemes—it also requires auditory object formation (Shinn-Cunningham, 2008), which relies on a successful interplay between myriad peripheral, central, and cognitive processes, whose age-related declines may not be coupled with ARSHL (Gordon-Salant et al., 2020). Thus, the genes that influence cocktail-party listening are not necessarily the same as those influencing ARSHL. To our knowledge, no previous studies have identified genomic loci influencing cocktail-party listening specifically, nor even demonstrated that this ability is heritable. The UK Biobank (Bycroft et al., 2018) measured speech-reception thresholds (SRTs) for digits mixed with babble in more than 100,000 people (see Dawes et al., 2014; Moore et al., 2014). Wells et al. (2019) reported that "[SRTs in this sample] did not yield clear heritability or association with age" (p. 760). Surprised by this finding, we reanalyzed the same data and found that the test–retest reliability of SRTs in the UK Biobank was poor ($r^2 \approx 0.1$). Further investigation revealed several methodological issues that in our view limit the utility of the UK Biobank dataset for exploring the genetic architecture of cocktail-party listening. In short, although recent studies have made considerable progress in elucidating the genetic etiology of ARSHL, including the identification of promising genomic loci, it is currently unknown whether the same genes—or any genes at all—influence cocktail-party listening.

Genetics studies involving related individuals must take care to avoid conflating genetic and environmental effects, as environmental factors can be shared or correlated among relatives. Arguably, normal aging is the strongest environmental factor to influence cocktail-party listening, as older listeners robustly perform worse than younger listeners on cocktail-party tasks even when matched in terms of HTs (e.g., Füllgrabe et al., 2015). Socioeconomic status (SES) is another important environmental factor that is associated with increased risk for hearing loss (Cruickshanks et al., 2015; He et al., 2018; Helvik et al., 2009; Lee et al., 2015; Wilson et al., 1999) and with poor SRTs (Dawes et al., 2014). SES reflects the aggregation of numerous putative environmental risk factors, such as occupational noise exposure (Cruickshanks et al., 2010), neighborhood noise levels (Dale et al., 2015), cardiovascular health (Clark et al., 2009), diet and obesity (Drewnowski, 2009), unhealthy behaviors (Pampel et al., 2010), and health-care availability (McMaughan et al., 2020); the effect sizes associated with these individual factors may be small to modest and therefore difficult to observe in small samples. Finally, noise exposure is an obvious potential environmental risk factor. If severe enough, noise exposure can impair cocktail-party listening by causing permanent noise-induced hearing loss. However, perhaps surprisingly, evidence for an association between typical amounts of lifetime noise exposure and cocktail-party listening is limited (e.g., Guest et al., 2018; Stamper and Johnson, 2015). This could be because measures of lifetime noise exposure, which are necessarily self-reported, are not sufficiently sensitive for this purpose (see Bramhall et al., 2019).

The primary aim of this study was to estimate the genetic contribution to solving the cocktail-party problem. We measured SRTs for simple sentences and time-reversed masker sentences, similar to previous studies (e.g., Bressler et al., 2014; Rhebergen et al., 2005), along with HTs and various other health and demographic variables, in a sample of 425 listeners. These listeners were randomly ascertained with respect to their hearing (i.e., some of them had hearing loss), represented a cross-section of the adult lifespan (18–91 years old), and belonged to large families. We applied variance component methods to estimate the narrow-sense heritability (Visscher et al., 2008) of SRTs with adjustments for various environmental factors. We also estimated the genetic correlation, or degree of overlap in genetic influences, between SRTs and HTs. Our aims were: (1) to provide evidence of a genetic contribution to SRTs, (2) to investigate whether SRTs and HTs are influenced by similar or distinct genetic factors, and (3) to differentiate the roles of genetic and environmental factors on SRTs.

RESULTS

SRTs were heritable

With adjustment for age, age^2, sex, age × sex, and age^2 × sex, the narrow-sense heritability (Visscher et al., 2008) of SRTs was $h^2 = 0.567$ [SE of parameter estimate = 0.133]. This value was significantly greater than 0 at a false-discovery rate (FDR)-corrected level [$\chi^2(1, N = 373) = 22.9$; p = 8.00×10^{-7}; $p_{FDR} = 3.87 \times 10^{-6}$]. Since heritability estimates from family studies can be overestimated due to shared environmental factors, we reestimated SRT heritability while simultaneously estimating the effects of shared households (birth, childhood, or

current), as is commonly performed in twin studies (Rijsdijk and Sham, 2002). Shared birth household explained a small amount of variance (c^2 = 0.131; SE = 0.131), but this was not significantly greater from 0 [χ^2(1, N = 373) = 0.935; p = 0.167; p_{FDR} = 0.230]. Importantly, SRT heritability remained significant with adjustment for shared birth household [h^2 = 0.512; SE = 0.146; χ^2(1, N = 373) = 14.7; p = 6.44 × 10⁻⁵; p_{FDR} = 1.70 × 10⁻⁴]. Neither shared childhood nor shared current household explained any variance or altered SRT heritability. Thus, our results suggest that roughly half the phenotypic variance of SRTs was due to genetic factors, before and after adjustment for age, sex, and shared households.

Although it was not one of the main aims of the study, we performed exactly the same analyses on better-ear average (BEA) HTs, which were significantly heritable with adjustments for age, sex, and shared households [h^2 = 0.518; SE = 0.140; χ^2(1, N = 378) = 16.5; p = 2.46 × 10⁻⁵; p_{FDR} = 8.92 × 10⁻⁵]. None of the shared household effects explained any variance or altered HT heritability.

SRT heritability was not driven by hearing loss

Since listeners were randomly ascertained with respect to their hearing, we expected some of them have hearing loss. Indeed, 96 listeners (23% of the sample; 95% confidence interval = 19%–27%) met the criterion for bilateral hearing loss, namely BEA HT > 25 dB hearing level. Of these individuals, 84 were over 45 years old and 41 were over 65 years old, suggesting that most cases of hearing loss in the sample were probably ARSHL. The observed rate of hearing loss in our sample was somewhat higher than the prevalence in the US adult population overall (~15%; Blackwell et al., 2014). It was slightly higher than that of an age-, sex-, and ethnically matched subsample of the National Health and Nutrition Examination Survey (NHANES; NCHS, n.d.), though not significantly so: prevalence in the NHANES subsample was 18%, and the 95% confidence interval around this estimate was 16%–21%, which overlapped with the confidence interval around the prevalence estimate in our sample.

We reperformed heritability estimation in the subsample of listeners without hearing loss (i.e., exclusively "normal-hearing" listeners). SRTs were significantly heritable in this subsample [h^2 = 0.630; SE = 0.166; χ^2(1, N = 286) = 16.1; p = 2.99 × 10⁻⁵; p_{FDR} = 9.63 × 10⁻⁵], as were HTs [h^2 = 0.437; SE = 0.168; χ^2(1, N = 285) = 7.86; p = 0.00253; p_{FDR} = 0.00458]. These results suggest that our prior main result, namely SRT heritability, was not driven by cases of clinical hearing loss.

Modest genetic overlap between SRTs and HTs

We estimated the genetic, environmental, and phenotypic correlations between SRTs and HTs. The genetic correlation was modest-to-medium and not significantly different from 0 at the FDR-corrected level [ρ_G = 0.392; SE = 0.180; χ^2(1, N = 379) = 3.72; p = 0.0538; p_{FDR} = 0.0821]. It was, however, significantly different from 1 [χ^2(1, N = 379) = 14.3; p = 7.94 × 10⁻⁵; p_{FDR} = 1.77 × 10⁻⁴]. Thus, while we cannot conclude that SRTs and HTs were significantly genetically correlated—or in other words, that the genetic effects on SRTs and HTs were overlapping—we can conclude that their genetic influences were not *perfectly* overlapping. In other words, partially distinct genetic factors influenced SRTs and HTs.

We also estimated phenotypic and environmental correlations between SRTs and HTs. The phenotypic correlation was significantly different from 0, but not very large [ρ_P = 0.325; SE = 0.0500; χ^2(1, N = 379) = 34.2; p = 4.93 × 10⁻⁹; p_{FDR} = 3.57 × 10⁻⁸]. The environmental correlation was small and not significantly different from 0 [ρ_E = 0.248; SE = 0.181; χ^2(1, N = 379) = 1.50; p = 0.220; p_{FDR} = 0.266].

Aging influenced SRTs

As shown in Figure 1A, SRTs increased (i.e., worsened) with advancing age, on average [χ^2(1, N = 373) = 78.3; p = 8.92 × 10⁻¹⁹; p_{FDR} = 1.29 × 10⁻¹⁷]. This aging effect was of medium-to-large size [Cohen's d = 0.682; SE = 0.0729]. Importantly, this effect did not bias our estimates of SRT heritability reported earlier because all models included age as a covariate. Although sex was included as a covariate as well, its effect was not significant [d = −0.0812; SE = 0.120; χ^2(1, N = 373) = 0.459; p = 0.498; p_{FDR} = 0.516]. Similarly, age², sex × age, and sex × age² were not significant but nevertheless included as covariates.

As shown in Figure 1B, aging also increased (i.e., worsened) HTs [d = 0.666; SE = 0.0657; χ^2(1, N = 378) = 91.2; p = 1.30 × 10⁻²¹; p_{FDR} 3.76 × 10⁻²⁰]. HTs were also larger in males than females, on average [d = −0.265; SE = 0.110; χ^2(1, N = 378) = 5.74; p = 0.0166; p_{FDR} = 0.0267]. Age², sex × age, and sex × age² were not significant covariates.
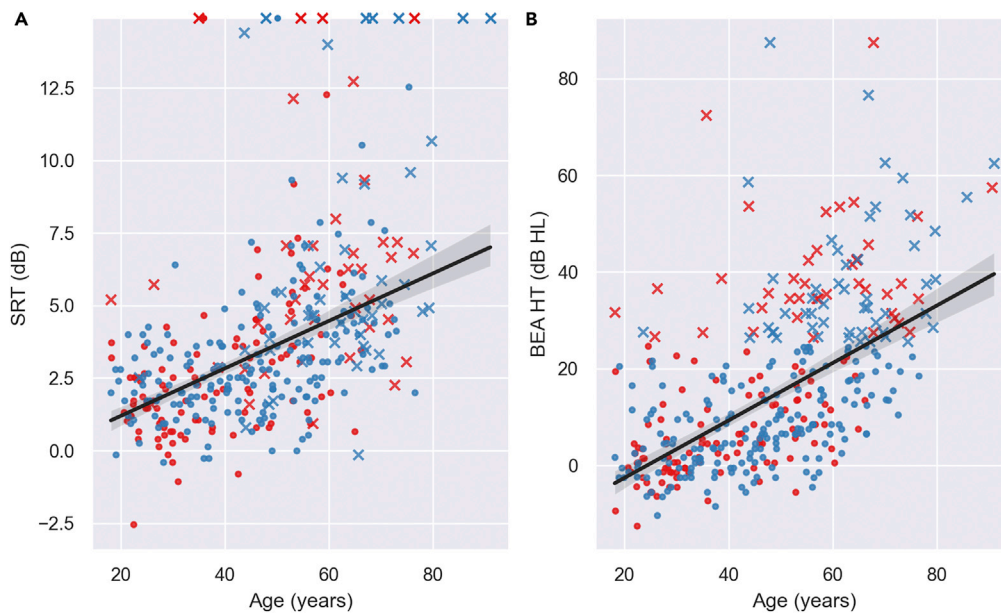
Figure 1. Decline of hearing abilities with advancing age

(A) SRTs as a function of age. Red symbols are females; crosses are hearing-impaired listeners. The black line is the best fit from a robust linear regression and the shaded region is its 95% bootstrap confidence interval. To enhance visual clarity, SRTs have been truncated at 14.9 dB in this panel; however, the untruncated data were used in the robust linear regression. Furthermore, all variance component methods were performed on transformed variables (see main text) and therefore not affected by outliers.

(B) BEA HTs as a function of age.

SES influenced SRTs

We measured SES in two ways. First, individual or personal SES was indexed via the Hollingshead score (Hollingshead, unpublished working paper, 1975). As shown in Figure 2A, SRTs were larger, on average, in listeners with lower (i.e., worse) Hollingshead scores [$d = -0.307$; SE = 0.0415; $\chi^2(1, N = 373) = 50.9$; p 9.69 × 10^{-13}; $p_{FDR} = 9.37 \times 10^{-12}$]. The same was true for HTs [Figure 2B; $d = -0.159$; SE = 0.0395; $\chi^2(1, N = 378) = 15.7$; p = 7.35 × 10^{-5}; $p_{FDR} = 1.77 \times 10^{-4}$]. Importantly, SRT and HT heritabilities remained significantly greater than 0 after adjustment for individual SES [SRTs: $h^2 = 0.264$; SE = 0.140; $\chi^2(1, N = 373) = 4.56$; p = 0.0163; $p_{FDR} = 0.0267$; HTs: $h^2 = 0.480$; SE = 0.143; $\chi^2(1, N = 378) = 13.6$; p = 1.14 × 10^{-4}; p_{FDR} 2.36 × 10^{-4}]. SRT heritability was attenuated after adjustment for individual SES. However, this observation should be interpreted cautiously because SES is itself a heritable trait (Trzaskowski et al., 2014). If similar genetic factors influence SRTs and SES, including SES as a covariate will remove the shared genetic component and cause SRT heritability to be underestimated. Indeed, when we performed an additional bivariate analysis of SRTs and individual SES, we found that they were strongly and significantly genetically correlated [$\rho_G = -0.924$; SE = 0.118; $\chi^2(1, N = 425) = 33.3$; p = 7.70 × 10^{-9}; $p_{FDR} = 4.47 \times 10^{-8}$].

The second measure of SES was the area deprivation index (ADI), an index of neighborhood SES (Kind and Buckingham, 2018). SRTs, but not HTs, increased with increasing (i.e., worse) ADIs, on average [Figures 2C and 2D; SRTs: $d = 0.137$; SE = 0.0440; $\chi^2(1, N = 361) = 9.51$; p = 0.00204; $p_{FDR} = 0.00395$; HTs: $d = 0.0625$; SE = 0.0419; $\chi^2(1, N = 366) = 2.22$; p = 0.136; $p_{FDR} = 0.197$]. SRT and HT heritabilities were largely unchanged after adjustment for ADI [SRTs: $h^2 = 0.536$; SE = 0.137; $\chi^2(1, N = 361) = 19.4$; p = 5.20 × 10^{-6}; $p_{FDR} = 2.15 \times 10^{-5}$; HTs: $h^2 = 0.498$; SE = 0.142; $\chi^2(1, N = 366) = 15.1$; p = 5.21 × 10^{-5}; $p_{FDR} = 1.51 \times 10^{-4}$].

No effects of other variables on SRTs

We explored the possible effects of numerous other health-related and environmental variables available in our sample, such as diagnoses of type 2 diabetes and metabolic syndrome, body mass index, waist circumference, smoking, alcohol consumption, and estimates of neighborhood noise levels caused by transportation surrounding listeners' current household addresses. None of these measures influenced either SRTs or HTs at the nominal or FDR-corrected levels.
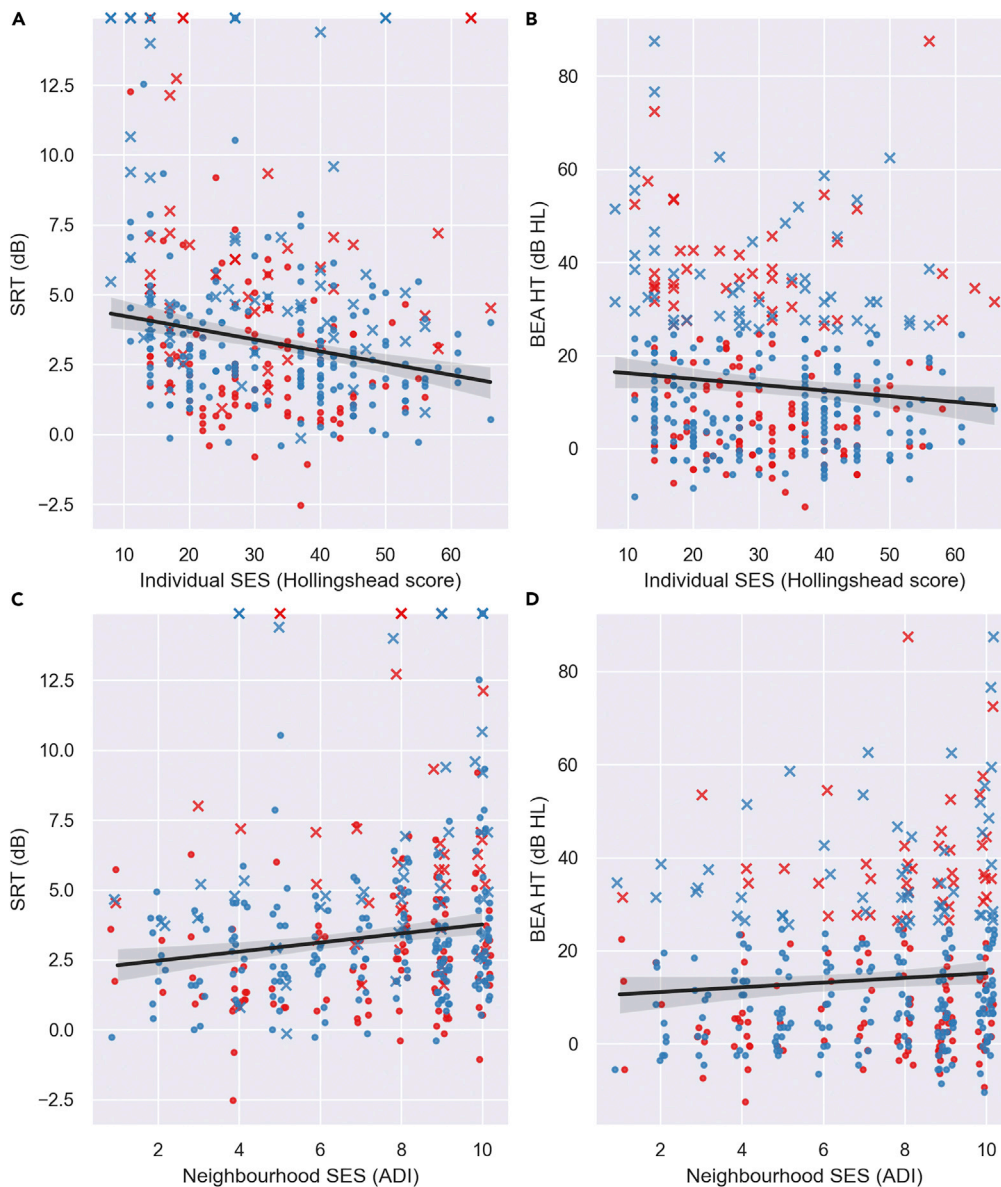
Figure 2. Influence of SES on hearing abilities

(A) SRTs as a function of individual SES, as indexed by Hollingshead scores, where a greater score indicates higher SES.

(B) BEA HTs as a function of individual SES.

(C) SRTs as a function of neighborhood SES, as indexed by state-level ADIs, where a greater score indicates lower neighborhood SES. T enhance visual clarity, a small amount of random jitter was applied to ADIs in this panel; however, all analyses, including the robust regression, were performed on the pre-jittered data.

(D) HTs as a function of neighborhood SES. In all panels, symbol shapes and colors, lines and shaded regions are consistent with Figure 1.

DISCUSSION

Summary of the main findings

We aimed to provide evidence for a genetic contribution to solving the cocktail-party problem. We measured SRTs in a community sample of listeners from multigenerational families who represented a cross-section of the adult lifespan, ranging from 18 to 91 years old. Since our sample was unascertained for hearing problems, it included listeners with hearing loss at roughly the same prevalence as another age-, sex-, and ethnically matched sample (NHANES). We found that SRTs were heritable. We also found

that HTs were heritable, consistent with previous family studies (Duan et al., 2019; Hendrickx et al., 2013; Kvestad et al., 2012; Raynor et al., 2009). Both abilities were heritable in the full sample as well as the clinically normal-hearing subsample. Heritability estimates were robust to shared environmental (i.e., household) effects.

We also investigated whether SRTs and HTs were influenced by similar or distinct genetic factors. These abilities were positively and significantly phenotypically correlated. The genetic correlation was also positive. However, it was not significantly different from 0, although it was significantly different from 1. In other words, SRTs and HTs were influenced by mostly distinct genetic factors.

Our final aim was to differentiate the roles of genetic and specific environmental factors on SRTs and HTs. Both abilities were influenced by aging and SES. Various other factors, such as cardiac health and neighborhood noise levels, did not appear to influence SRTs. Given that the effect sizes of these specific individual risk factors tend to be small-to-modest in large epidemiological samples, it is not surprising that we did not observe them here. SRTs and HTs remained heritable after adjustment aging and SES.

Implications for future genetics studies of hearing loss

The findings represent an initial step toward identifying specific genes or gene networks that influence real-world hearing abilities or problems besides clinically defined hearing loss (i.e., reduced sound sensitivity). In this study, as in other quantitative genetics studies, the goal was not to identify associations between specific genetic variants and such abilities; consequently, the results do not tell which genes are involved in cocktail-party listening. However, the results do suggest that such genes exist and are potentially discoverable.

As adult-onset hearing problems are probably largely polygenic, small-scale case–control or family studies that were previously successful in delineating the genetic architecture of rare genetic disorders, such as prelingual hearing loss (Shearer et al., 2017), are unlikely to be successful. An alternative approach is to perform GWAS, particularly when conducted in large samples to ensure sufficient power to detect small effects. Recently, several GWAS have identified numerous genomic loci for ARSHL (Fransen et al., 2015; Girotto et al., 2011; Hoffmann et al., 2016; Ivarsdottir et al., 2021; Nagtegaal et al., 2019; Van Laer et al., 2010; Vuckovic et al., 2015). Another large study implicated several genomic loci for self-reported hearing problems and hearing-aid use in people with unknown audiometric profiles (Wells et al., 2019). Given that HTs were unavailable in the latter sample, the group with self-reported hearing problems was probably a mix of individuals with and without clinical hearing loss. Our conclusion of a lack of complete genetic overlap between SRTs and HTs (based on the modest genetic correlation between these traits) complicates the interpretation of these results. The literature is currently lacking a large-scale genetics study where both SRTs and HTs were measured in the same listeners, which would allow loci for one ability to be distinguished from loci for the other.

Implications for hearing studies

It is widely accepted that individuals can struggle to solve the cocktail-party problem without meeting the criteria for clinical hearing loss. Indeed, "hidden hearing loss" is a popular term describing such problems (Schaette and McAlpine, 2011). Despite considerable recent interest in hidden hearing loss, its biological mechanisms remain unclear. The most promising putative biological mechanism is cochlear synaptopathy (Liberman and Kujawa, 2017; Plack et al., 2016). Briefly, Kujawa and Liberman (2009) showed that when mice are exposed to moderate noise levels that cause temporary HT shifts, they permanently lose afferent connections between inner hair cells and auditory nerve fibers. This synaptopathy is selective to low spontaneous-rate fibers that are thought to encode suprathreshold sounds (Furman et al., 2013), suggesting that synaptopathy may impair suprathreshold discrimination abilities, including cocktail-party listening, while preserving sound sensitivity. Importantly, cochlear synaptopathy also occurs as part of the normal aging process in mice raised without noise exposure (Sergeyenko et al., 2013) as well as in humans, according to postmortem studies (Wu et al., 2019).

Our findings to do not speak directly to cochlear synaptopathy because we did not measure peripheral auditory function. However, they may shed some light on the debate surrounding its role in hidden hearing loss. While there is compelling evidence for noise-induced cochlear synaptopathy in nonhuman animals, potentially damaging noise levels cannot be delivered to, nor synapses counted in, living human ears.

Recently, several electrophysiological correlates of cochlear synaptopathy have been developed (reviewed by Bharadwaj et al., 2019; Plack et al., 2016). While such assays correlate with performance on laboratory tasks in normal-hearing listeners (e.g., Bharadwaj et al., 2015), it has proven difficult to find associations between them and lifetime noise exposure (Bramhall et al., 2019). Measurement insensitivity may play a role; that is, putative correlates of cochlear synaptopathy and/or lifetime noise exposure may be difficult to measure with sufficient precision. However, our results suggest another possibility, namely the existence of large, genetically determined individual differences in cocktail-party listening abilities—and by extension, the possible biological correlates of those abilities, such as cochlear synaptopathy—that are *necessarily irrespective of prior exposure to environmental risk factors*. Thus, environmental relationships between cochlear synaptopathy and aging/noise exposure may be obscured by substantial genetic effects, especially in genetically heterogeneous samples.

Awareness of this possibility has the potential to improve detection of environmental influences on aspects of auditory function. For example, there is growing support for the view that cochlear synaptopathy may occur before, and possibly lead to, hair-cell or auditory nerve neuropathy (Liberman and Kujawa, 2017). Therefore, cochlear synaptopathy could actually be an early warning sign of later clinical hearing loss. If so, future studies may achieve better results by recruiting listeners at high genetic risk of clinical hearing loss, such as people with significant family history ARSHL or those at with high polygenic risk scores for ARSHL (Cherny et al., 2020), although the positive predictive value of the latter technique would need to improve dramatically before this becomes a realistic strategy (Wald and Old, 2019). The basic idea of assessing high-risk individuals before disease onset has enabled researchers to characterize the prodromes of other heritable neurodegenerative disorders, such as Huntington disease (Stout et al., 2011), Parkinson disease (Postuma and Berg, 2019), and Alzheimer disease (Giunta et al., 2008), but to our knowledge, it has not yet been applied to hearing problems.

Environmental factors

The influence of normal aging on hearing abilities has been extensively studied (Gordon-Salant et al., 2020; Humes and Dubno, 2010). It is well known that hearing loss is more common in listeners with lower individual SES or people living in lower-SES areas (Cruickshanks et al., 2015; He et al., 2018; Helvik et al., 2009; Lee et al., 2015; Wilson et al., 1999). Furthermore, Dawes et al. (2014) reported an association between SRTs and the Townsend deprivation index, a measure of neighborhood SES similar to the ADI (Kind and Buckingham, 2018; Norman, 2010). It is difficult to identify the specific causal factors driving the relationships between SES and SRTs/HTs because SES is correlated with many potentially important environmental variables. An obvious possible factor is occupational noise exposure, which we were unable to measure in our sample. We also considered the roles of neighborhood noise levels (based on listeners' geocoded current households) as well as several measures of physical and cardiovascular health, but did not find associations between HTs/SRTs and any of these factors.

Limitations of the study

A potential limitation of this study was that we used time-reversed maskers. Pilot work suggested that time-reversed maskers were necessary to produce data that were reliable enough for quantitative genetic analysis in this sample. In an early version of the task, the target sentence was presented with time-forward maskers spoken by different talkers and the target sentence was distinguished from the maskers by the first word ("Jane"). This version of the task often produced floor effects in naive listeners in our sample even after practice. Another version employed maskers that were spatially separated from targets via interaural time differences, but this also produced floor effects. The critical factor seemed to be that time-forward maskers were intelligible, which had the undesirable side effect of occasionally confusing listeners about the task demands. For example, sometimes listeners would report whichever sentence they heard the best, regardless of whether it was the target or a masker. Other times, listeners would try to report all three sentences. Time-reversed maskers eliminated these sources of confusion because they were never intelligible, greatly reducing floor effects and producing SRTs that were better suited to quantitative genetic analysis.

Despite being more suitable for our purposes, one could argue that SRTs measured with time-reversed maskers have less ecological validity than SRTs measured with time-forward maskers because listeners do not encounter time-reversed speech in the real world. This limitation may be important if the masking caused by time-reversed maskers is substantially different in nature to that caused by time-forward

maskers. Kidd et al. (2016) considered this issue in detail by conducting a cocktail-party listening experiment using time-forward maskers (baseline condition), masker talkers of the opposite sex to the target talker (sex condition), maskers spatially separated from the target (spatial condition), and time-reversed maskers (reversed condition). The authors also included conditions where the stimuli were manipulated using ideal time–frequency segregation (ITFS), which essentially removed portions of the maskers that acoustically overlapped with the targets. SRTs were lower (better) in the sex, spatial, and reversed conditions than the baseline condition, as expected. Crucially, ITFS processing did not fundamentally change the pattern of results, suggesting that the principles governing sex-, spatial-, and reverse-based release from masking were all similar (i.e., all "informational masking;" see Brungart, 2001). Furthermore, individual differences were correlated across the three masking-release conditions. These results suggest that the advantage to cocktail-party listening provided by using time-reversed maskers is similar in nature to the advantages that come from cues that exist in the real world, such as sex and spatial differences.

Another limitation was that SRTs and HTs were measured using a consumer-grade equipment, namely a laptop with an integrated sound card. Moreover, testing was performed in an ordinary quiet testing room rather than a sound-attenuated booth. These features make it difficult to compare our listeners' raw SRTs and HTs to those from other psychoacoustics studies, and probably caused them to be higher overall as well adding some amount of additional measurement error. However, importantly, since the data were transformed prior to analysis, absolute SRT and HT values did not influence our results. Furthermore, our measures were clearly sensitive enough to detect genetic and environmental effects on both abilities.

The present study is small by modern genomics standards (cf. the UK Biobank) and focused on a single ethnic group. Despite the modest sample size, the extended pedigree design provided sufficient statistical power to detect the heritable component of variance in SRTs. However, it is possible that a larger sample could provide statistical evidence that SRTs and HTs are genetically correlated. We consider it extremely unlikely that conducting the study using a different ethnic group would have produced qualitatively different results, such as markedly stronger or weaker heritabilities or correlations.

Finally, this study framed genetic and environmental factors as two distinct classes of variables that independently contributed to cocktail-party listening. However, the biological consequences of environmental stress may be heritable—in other words, cocktail-party listening may be susceptible to gene-by-environment interactions. We have previously provided statistical evidence for such interactions, specifically gene-by-age interactions, on cognitive abilities and brain anatomy in multigenerational families (Glahn et al., 2013). We intend to explore whether cocktail-party listening is influenced by similar gene-by-environment interactions in future studies.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
NHANES continuous cycles (1999–2018)	National Center for Health Statistics, n.d.	https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx
Software and algorithms		
SOLAR	Almasy and Blangero (1998)	https://hpc.nih.gov/docs/solar-8.1.1/00.contents.html

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Sam Mathias (samuel.mathias@childrens.harvard.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The IGAB dataset reported in this study cannot be deposited to a public repository because it contains potentially identifiable information. Anonymized subsets of the data will be shared by the lead contact upon request. All original code and any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

As part of Imaging Genomics of the Aging Brain (IGAB) project, 425 listeners (255 females), ranging from 18 to 91 years old (median = 47.6 years), were recruited from 48 pedigrees. Of these individuals, 255 were female. Pedigrees varied in size, the largest having 88 members. Reported familial relationships were empirically verified based on autosomal markers. No recruitment or screening was performed based on any disorder or ability, including those related to hearing. All listeners provided written informed consent on forms approved by the institutional review board (IRB) at the data-collection site, University of Texas Health Science Center at San Antonio, as well as IRBs at the University of Texas Rio Grande Valley and Boston Children's Hospital.

METHOD DETAILS

Recruitment details

All IGAB participants participated in at least one of the following previous studies: the San Antonio Family Heart Study (SAFHS; Mitchell et al., 1996); the San Antonio Family Gallbladder Study (SAFGS; Duggirala et al., 1999); and the Genetics of Brain Structure and Function Study (GOBS; Olvera et al., 2011). SAFHS occurred across three recruitment phases between 1992 and 2007. To be eligible for SAFHS, an individual had to be of Mexican American ancestry, aged 40–60 years, have a spouse willing to participate, and have at least six adult (>16 years old) offspring and/or siblings. SAFHS also recruited the spouses of these participants (if they were Mexican American), their first-, second-, and third-degree adult relatives, and Mexican American spouses of those relatives. SAFGS was conducted between 1998 and 2001 and recruited additional Mexican American families in a similar way, except that the initial proband always had type-2 diabetes. Since this disorder has a lifetime prevalence approaching 30% in this population, the recruitment strategy employed in SAFGS represented effectively random sampling for other diseases, behaviors, and abilities. GOBS was conducted between 2006 and 2014 and re-recruited SAFHS and SAFGS individuals, as well as their previously unrecruited adult offspring. GOBS recruited 1,904 individuals in total. IGAB, which began in 2018, recruited exclusively from the pool of previous GOBS participants.

Overview of the assessments

All IGAB participants were instructed to visit the laboratory so that phenotypic data could be collected. Usually, all phenotypic data were collected during a single visit. All IGAB participants attempted to complete the hearing test, which measured HTs, and the cocktail-party listening task, which measured SRTs, during their visit. These tests were completed under supervision from a trained administrator in a quiet testing room using a laptop with a touchscreen display and headphones (Sennheiser HD 25 Pro). Other demographic variables, health and physical variables, and biological samples for future analyses were collected during the visit.

Given that the protocol did not involve prior screening for hearing impairment, several listeners arrived at their assessment using hearing aids. These individuals were considered to have hearing loss and their HTs and SRTs were excluded from all analyses. No listeners used cochlear implants.

Hearing test

The hearing test measured HTs for 0.5-, 1-, 2-, 4-, 8-, and 12.5-KHz pure tones in both ears. Each trial in the hearing test had a fixed 2-s interval which equiprobably contained or did not contain a monaural 1-s pure tone whose amplitude was modulated at 100% depth using a 2-Hz full-wave rectified sinusoid. Listeners pressed the space bar whenever they heard a tone. Trials were organized into separate blocks for each frequency and ear. The lowest frequency tested was 0.5 kHz because previous work suggests that HTs measured inside and outside of a sound-attenuated chamber are largely equivalent at or above this frequency, whereas lower-frequency HTs may be unreliable (Whitton et al., 2016). Within a block, the first tone had a fixed level of 60 dB hearing level (HL) and the levels of subsequent tones were manipulated using a single interval adjustment matrix (Kaernbach, 1990) with an adjustment factor of 10 dB up to the second reversal and 4 dB afterward. Blocks were terminated after six reversals. HTs were defined as the quietest sound heard per frequency and ear. Better-ear average (BEA) HTs were calculated using all frequencies except 12.5 kHz.

Cocktail-party task

We carried out pilot work to evaluate the suitability of various existing cocktail-party tasks in our sample. We first considered the QuickSIN (Killion et al., 2004) but worried that due to its inclusion of low-frequency words and semantically predictable sentences, performance would have been influenced by language and reasoning skills. We also considered the digit triplet test (Dawes et al., 2014; Moore et al., 2014), but as mentioned in the introduction, this task yielded unreliable data in a previous study. Prior psychoacoustical studies provide several paradigms that mitigate the above limitations but are often inefficient in terms of overall duration due to repetition of several redundant words per trial (e.g., Bolia et al., 2000).

We therefore opted to develop a task inspired by the work of Kidd and colleagues (Kidd et al., 2008). On each trial of the task, listeners heard a target sentence starting with the name "Jane" followed by four variable words (e.g., "Jane bought two red gloves."). There were eight possible variable words per position (verbs: "bought," "found," "gave," "heard," "held," "kicked," "saw," "threw;" numbers: "two" to "ten" excluding "seven;" adjectives: "big," "blue," "cold," "hot," "black," "old," "red," "small;" nouns: "bags," "cards," "gloves," "hats," "pens," "shoes," "socks," "toys"). Target sentences were presented at an average sound pressure level (SPL) of 60 dB and mixed with two random masker sentences constructed from the same corpus but with a different name ("Pat" and "Sue") and with the constraint that no word could occur more than once on a given trial. Masker SPLs were manipulated to achieve a desired signal-to-noise ratio (SNR) with the targets. Maskers were time-reversed and aligned to have simultaneous onsets with the targets. Sounds presented diotically and synthesized using Google WaveNet (Oord et al., 2016). Target sentences were synthesized using a neutral-accented United States male voice model and maskers were synthesized using two different male voice models. Listeners reported the variable words per target sentence via a graphical user interface on the touchscreen with one button per variable word. To lessen the burden on listeners' reading abilities, each button also contained a pictorial representation of the corresponding word.

On the first trial, the SNR was + 40 dB (i.e., maskers were 20 dB SPL). On following trials, SNRs were decreased and increased by 2 dB for every correct and incorrect selection, respectively, on the immediately preceding trial. For example, if a listener selected three variable words correctly (i.e., made one error) on a trial, the SNR on the next trial was 40 − 2 − 2 − 2 + 2 = 36 dB. It is straightforward to show that this procedure

converges asymptotically on the SNR value that yields a 50% chance of a correct response assuming a constant psychometric function (Levitt, 1971). The task was always terminated after 30 trials. SRTs were estimated by taking the mean of all SNR values excluding the SNR on the first trial, which was always 40 dB and therefore uninformative, and including the theoretical 31st trial, whose SNR could be calculated based on listeners' responses to the 30th trial.

Geocoding

Household information was used both in the estimation of shared environmental effects and to calculate neighborhood SES. A listener's current household was defined as where they lived at the time of assessment, or their previous address if they had lived at the current address for less than 6 months. Childhood household was defined as where they lived the longest prior to age 18 years, and birth household was defined as their first address.

Addresses were self-reported and converted to geographic coordinates via Google's geocoding application programming interface (API; Google, n.d.). If addresses were in the USA, Federal information processing system (FIPS) codes were obtained via the Federal Communication Commission's API (Federal Communication Commission, n.d.). FIPS codes were used to obtain ADI (Kind and Buckingham, 2018) of each address.

SES

As a measure of individual SES, the Hollingshead four-factor index (Hollingshead, 1975), which is based on self-reported education and employment information, was calculated per listener. Listeners' state-level ADI based on their current household (all listeners' current addresses were within or close to San Antonio, TX) was used as a measure of neighborhood SES. If an address belonged to more than one block group, ADI for that address was defined as the mean of ADIs over all block groups to which it belonged. The ADI provides a value between 1 and 10 (at the state level) and between 1 and 100 (at the national level) representing neighborhood socioeconomic disadvantage, where a large number reflects greater disadvantage, for block groups based on 2019 census data. If a location belonged to more than one block group, the final ADI was defined as the mean ADI across block groups.

QUANTIFICATION AND STATISTICAL ANALYSIS

Quantitative genetic analysis

Our first aim was to provide evidence of a genetic contribution to cocktail-party listening. To this end, BEA HTs and SRTs were rank-based inverse-normal transformed to ensure that they were normally distributed and reduce the influence of outliers, then analyzed with variance component models (Lynch and Walsh, 1998). Under the simplest of such models, it is assumed that the focal trait has a multivariate normal distribution whose mean, denoted by $\boldsymbol{\mu}$, is given by $\boldsymbol{\mu} = \boldsymbol{X\beta}$, where $\boldsymbol{X}$ is a design matrix of covariates and $\boldsymbol{\beta}$ is a vector of regression coefficients. All models included an intercept, age, age^2, sex, age-by-sex and age^2-by-sex interactions. The covariance matrix, denoted by $\boldsymbol{\Omega}$, is given by $\boldsymbol{\Omega} = 2\boldsymbol{\Phi}\sigma_G^2 + \boldsymbol{I}\sigma_E^2$, where $\boldsymbol{\Phi}$ is the matrix of kinship coefficients between individuals, σ_G^2 is the variance of the additive genetic component, $\boldsymbol{I}$ is an identity matrix, and σ_E^2 is the variance of the residual component. The proportion of phenotypic variance explained by additive genetic effects, or narrow-sense heritability (Visscher et al., 2008), denoted by h^2, is given by $h^2 = \sigma_G^2/(\sigma_G^2 + \sigma_E^2)$. After fitting, we may test whether $h^2 > 0$ by fitting a null model with the constraint $h^2 = 0$ and performing a one-tailed likelihood-ratio test (LRT).

Heritability estimates from family studies may be biased due to conflating genetic factors with environmental factors that are shared among biological relatives. One approach to mitigating this concern, commonly used in twin studies (Rijsdijk and Sham, 2002) but applicable to any family study, is to introduce an additional variance component to the model. Under the extended model, $\boldsymbol{\Omega} = 2\boldsymbol{\Phi}\sigma_G^2 + \boldsymbol{M}\sigma_C^2 + \boldsymbol{I}\sigma_E^2$, where $\boldsymbol{M}$ and σ_C^2 are the correlation matrix and variance, respectively, of the additional component. Typically, the additional variance component represents shared households, such that values in $\boldsymbol{M}$ are equal to 1 if the corresponding pair of individuals in the sample share a household, and equal to 0 otherwise. The phenotypic variance explained by the additional component, denoted by c^2, is given by $c^2 = \sigma_C^2/(\sigma_G^2 + \sigma_C^2 + \sigma_E^2)$, and heritability is redefined as $h^2 = \sigma_G^2/(\sigma_G^2 + \sigma_C^2 + \sigma_E^2)$. After fitting such a model, we may test whether $c^2 > 0$ or $h^2 > 0$ via separate one-tailed LRTs. Here, we tested whether HTs or SRTs were

influenced by shared current, childhood, or birth households, and whether these effects influenced heritability estimates.

Our second aim was to investigate whether HTs and SRTs are influenced by similar or distinct genetic factors. To this end, we fitted a bivariate variance component model. Such a model considers two focal traits simultaneously and estimates separate covariate effects on both traits, heritability of both traits, and correlations between traits. There are three distinct kinds of correlation under this model: genetic, environmental, and phenotypic. The genetic correlation, denoted by ρ_G, is the correlation between the latent additive genetic effects, and reflects the degree to which the genetic factors influencing both traits overlap. The environmental correlation, denoted by ρ_E, is the correlation between the latent residual effects. Since environmental effects include measurement error, environmental correlations can be difficult to interpret. The phenotypic correlation, denoted by ρ_P, is the correlation between the observations, and may be interpreted in the same way as a Pearson's product-moment coefficient. We may test whether any of these correlations differ from a certain value, such as 0 or ± 1, by fitting a null model (e.g., where $\rho_G = 0$) and performing a two-tailed LRT.

Our third aim was to examine the role of specific environmental factors on HTs and SRTs. Such effects were estimated by including environmental variables as additional fixed-effect covariates within the design matrices (X) of univariate variance component models. Such models also provide a heritability estimate for the focal trait adjusted for the specific environmental factor, assuming that the environmental factor has no genetic component that overlaps with the trait. The effect size of the environmental factor is given by the corresponding element within β, and may be tested by fitting another model without the factor and performing a two-tailed LRT.

Trait transformations and model fitting via maximum-likelihood estimation were performed using SOLAR (Almasy and Blangero, 1998). All p values were corrected for multiple comparisons by applying a single-step FDR correction (Benjamini and Hochberg, 1995).

Prevalence of hearing loss

Listeners were considered to have bilateral hearing loss if they wore hearing aids or had BEA HTs <25 dB hearing level. To estimate the population prevalence of bilateral hearing loss in this community, we applied a bootstrap procedure to the audiometric and demographic data from 14,076 adult listeners of Hispanic/Latino ancestry from the continuous cycles (1999–2018) of the National Health and Nutrition Examination Survey (NHANES; NCHS, n.d.). Per iteration of this procedure, an NHANES listener was randomly selected with replacement for every one of our listeners, ensuring that the NHANES listener was the same sex and age to the closest year as our listener. The proportion of hearing-impaired listeners in the NHANES subsample (BEA HT < 25 dB hearing level) was recorded and the process was repeated 10,000 times. The prevalence estimate was defined as the mean subsample proportion. The lower and upper limits of the 95% confidence interval around the NHANES prevalence estimate were defined as the 2.5th and 97.5th percentiles, respectively, of the subsample proportions. Wilson's method without continuity correction was used to estimate the 95% confidence interval around the prevalence estimate in our sample.