



# On variability and genes: inter-individual differences in auditory brain function

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We are embarking on a new frontier in human auditory neuroscience, integrating rapidly advancing neurophenotyping approaches to brain research, with genetic and genome-wide studies. A variety of human neuroimaging and electrophysiological techniques allows to analyze brain structure, function, and neurochemistry in the same individual. As human neuroscience and genetics/genomics research goals converge, the focus is shifting toward understanding how individual variations in auditory neurobiology are shaped by genes and experience, and how these mechanisms influence normal behavior and disease risk.

By correlating neurogenetics with imaging or electrophysiological neurophenotyping techniques, researchers have identified molecular contributions to variation in auditory brain structure and function (Leonard et al., 2002; Liu et al., 2009; Lamminmäki et al., 2012). The approach termed imaging genetics addresses the impact of genetic variations, often single nucleotide polymorphisms, on the individual neurophenotype derived from structural or functional MRI, PET, MR spectroscopy, or a combination of these neuroimaging techniques (for recent reviews see Bigos and Weinberger, 2010; Thompson et al., 2010). Imaging genetics has already generated important contributions to our understanding of the normal and pathological brain, including the structure and function of regions involved in the processing of auditory stimuli (Liu et al., 2009; Pinel et al., 2012; Wilcke et al., 2012). Electrophysiologists have adopted this approach and successfully associated amplitudes and latencies of evoked or event-related electromagnetic brain activity with genetic markers (e.g., Gallinat et al., 2003). Majic et al. (2011) stimulated healthy participants with pairs of sound clicks and studied the P1 (P50) and N1 (N100) components of the auditory evoked potential. Stimulation with two or more identical acoustic stimuli

in fast succession, separated by a silent interval long enough for a recovery of the P1 and N1 components, results in a reduction of the second relative to the first P1 and N1 amplitude, termed auditory decrement, gating, or habituation (Rosburg et al., 2004; Sörös et al., 2006, 2009). In the study of Majic et al. (2011), individual auditory decrement was correlated with the widely studied COMT Val(108/158)Met polymorphism, a genetic variation that modulates the dopamine system which is essential for prefrontal cortex processing capacity in general and the filtering of sensory information in particular. Participants with the Met/Met genotype showed a smaller decrement of the N1 component compared with carriers of the Val/Met or Val/Val polymorphisms. The Met/Met genotype is associated with higher performance in tests of prefrontal functions. In contrast, no significant effect of the COMT genotype was observed for the P1 decrement. Similarly, the amplitude decrement of the P1 was not modulated by selected single nucleotide polymorphisms in COMT, BDNF, or NRG1 in psychiatric patients, their healthy relatives and controls (Shaikh et al., 2011). However, variants in the promoter region of CHRNA7 and in SLCA3, genes coding for the alpha 7 nicotinic acetylcholine receptor subunit and a dopamine transporter (DAT1), respectively, have been associated with individual differences in the amplitude decrement and latency prolongation of P1 in response to repeated sound stimulation (Leonard et al., 2002).

Auditory perceptual processing deficits are a common feature of psychiatric, neurologic, and communication disorders, and altered neurophenotypes have been identified in these clinical populations using neurophysiological and imaging genetic approaches (Leonard et al., 2002). In dyslexic patients, a variant of the ROBO1 gene that guides axons crossing the midline of the central nervous system has been associated

with abnormal auditory evoked MEG responses to complex amplitude modulated sounds presented binaurally (Lamminmäki et al., 2012). Dyslexia risk polymorphisms (KIAA0319/TTRAP/THEM2 locus) have also been related to altered fMRI activity in the superior temporal sulcus, an area associated with speech sound processing (Pinel et al., 2012). With respect to psychiatric disease, a recent imaging genetics study using genomic linkage analysis and fMRI found a significant relationship between gene variants and parietal lobe activity in response to rare and frequent sound stimuli in healthy individuals and schizophrenic patients (Liu et al., 2009). In addition to genetic findings in patients with these diseases, a range of electrophysiological, neuroimaging, and behavioral auditory processing differences have been found in their unaffected relatives, making these measures potential endophenotype candidates for gene discovery.

Success in this new field of non-invasive research into the genetic determinants of brain structure and function hinges on our ability to detect and interpret inter-individual phenotype differences. Inter-individual differences may vary along a continuum, or form subcategories within a subject group or diagnostic category. McArthur and Bishop (2005) found inter-individual differences in auditory processing for children diagnosed with specific language impairment, with only a subset of the impaired group displaying behavioral or auditory evoked potentials different from controls. Both within and between subject variability may also be addressed by adhering to inclusion/exclusion criteria that reduce the effects of confounding factors. For example, because the auditory system exhibits experience-related plasticity, subjects should be screened for a history of auditory deprivation (e.g., childhood ear infections) or learning (e.g., musical training).

A major challenge of functional neuroimaging and electrophysiology is to separate behaviorally related brain activity from unrelated processes. In order to separate signal from noise, researchers average brain activation across several trials during scalp recordings of evoked electric or magnetic responses or measurements of task-related blood-oxygenation level dependent responses in functional magnetic resonance imaging (BOLD fMRI). Additional techniques include *in vivo* bio-amplifier technology, signal filtering techniques, and averaging protocols that maintain a specific signal-to-noise ratio, methods that are particularly valuable for recording low amplitude subcortical auditory system activity (Sininger, 1993; Munro et al., 2011). To further increase signal-to-noise ratios, most studies calculate and interpret group averages of brain activation, an approach that has proven fruitful to eliminate artifactual data and brain activity unrelated to the experimental paradigm. However, researchers need to acknowledge that group averages of brain activation data may conceal highly relevant differences in individual phenotypes of brain function and limit research on the neural basis of such differences. Averaging across individuals or even independent studies, using recently developed techniques for quantitative meta-analysis of neuroimaging data (Kober and Wager, 2010; Laird et al., 2011; Yarkoni et al., 2011) may conceal significant inter-individual differences in brain function. The publication of single-subject data in electrophysiological and neuroimaging papers, along with group averages, is a first but crucial step to emphasize the importance of inter-individual differences in human neuroscience. Publication of supplementary figures and tables, even entire data sets, on a journal's web site along with the corresponding article and open repositories for data sharing (Visscher and Weissman, 2011) allow the presentation of single-subject data and will help to study and discuss the phenomenology of individual brain function and fuel research on the genetic mechanisms underlying these phenomena. Analyses that explore the relationship between inter-individual auditory neurophenotype differences and the group average, or between individual responses and genetic variability are providing new insights into the neural networks involved in human communication and the genetic bases of related communication disorders

(Bishop et al., 2007; Pinel et al., 2012). Such strategies are critical for understanding the genetic determinants of normal variability in healthy populations, and how these contributions might contribute to complex disease.

Of paramount importance, the test-retest reproducibility of a given neuroimaging or electrophysiological experiment has to be known. In studies that investigate primary sensory cortices, non-invasive electrophysiological recordings using EEG and MEG appear to be reasonably reproducible. Repeated recordings of auditory evoked electric potentials and magnetic fields demonstrated a relatively high reproducibility of the auditory N1 amplitude, latency, and dipole location (Virtanen et al., 1998; Sörös et al., 2006), comparable to the reproducibility of source localizations found for somatosensory evoked magnetic responses (Schaefer et al., 2004). However, factors that limit the reproducibility of neuroimaging and electrophysiological data, attention and fatigue, for example, need to be evaluated and, as much as possible, controlled for. Recently, cognitive effort and attention have been associated with the 5-HTTLPR polymorphism occurring in the promoter region of the SLC6A4 serotonergic transporter gene and related to inter-subject variability in the N1 auditory evoked electrical potential (Enge et al., 2011). The test-retest reproducibility of fMRI data is still under intense debate (Bennett and Miller, 2010). In any case, there is convincing evidence that variability between subjects is by far higher than within-subject variability (Miller et al., 2009). Most important for clinical researchers, reproducibility of measurements needs to be established for the population under investigation, e.g., children, elderly individuals, or patients with specific disorders. Reproducibility of a given task in these populations is not necessarily comparable to reproducibility in healthy young adults, the notorious participants of neuroimaging research (Bennett and Miller, 2010). Controlling for potential confounding factors that affect within-subject variability is vital when the goal is to correlate molecular genetic variation with inter-individual differences in auditory system processing.

Although human imaging and electrophysiological responses are proving to be reliable neurophenotypes, even potential endophenotypes, these traits are complex and under variable polygenic and

environmental control. The challenge is to target the most sensitive and complementary techniques and use them to generate an informative auditory neurophenotype, one that reflects inter-individual differences and the biological context from which an individual's complex traits emerge. How do we select the most appropriate neurophenotyping strategies? New physiological techniques using simple and complex sound stimuli, including speech, are now available to assess the auditory periphery and brainstem in addition to cortical level activity (for a review, see Skoe and Kraus, 2010). Because these techniques can probe inner ear and neural activity with high temporal resolution, they provide a complementary approach to neuroimaging techniques which provide high spatial resolution at the cortical level, but limited sensitivity to subcortical activity or temporal aspects of auditory processing. Currently, few imaging genetics studies consider peripheral and subcortical contributions to auditory processing, despite recent studies implicating abnormal processing at these levels in a variety of disorders. If the goal is gene discovery, we must identify complementary neurophenotyping measures that are more sensitive to inter-individual differences than the clinical diagnosis, and also proximal to the biological substrates of disease in affected patients.

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