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Relating Stroke Pathology to Individual Binaural Perception

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[1] Bence, Peter, (2014). *Cry me a river by Justin Timberlake*, available at https://www.youtube.com/watch?v=V69ntkR3YBY

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Summary

The sense of hearing is used to detect, identify, and localize sound sources. The interaural differences (i.e., the differences between the two ears) in time and level of incoming sounds can be used to localize sound sources and segregate auditory streams. Thus, hearing in general, and binaural hearing in particular, contribute to navigating the world successfully. In humans and other mammals, the first stage of processing of binaural information is found in the brainstem. In addition to these brainstem nuclei, many other processing structures on the primary auditory pathway and brain areas outside the primary auditory pathway are involved in providing spatial awareness and enhancing auditory perception. Pathological changes in any of these stages can lead to difficulties in binaural hearing tasks, but research on the individual consequences of such pathologies is still inconclusive. Studying hearing abilities in clinical populations is relevant to enable effective diagnosis and individualized rehabilitation. Impaired individuals can be helped best if both behavioral effects and underlying pathologies are thoroughly understood.

Ischemic stroke is a highly prevalent medical condition in which the blood flow through the brain is disrupted by an acute blockage of blood vessels. As a result, specific brain areas are not supplied with oxygen and nutrients anymore. This can lead to various symptoms, such as motor deficits, cognitive decline, and sensory impairments. Adverse effects of stroke lesions on binaural perception have been shown in several studies. The majority of these studies have been conducted in the chronic phase of stroke and included only patients with a lesion of one specific brain area. However, conducting such experiments in the acute phase and including a variety of lesion locations would allow insights into the underlying encoding and decoding of binaural information. Furthermore, there is a lack of literature on the recovery of impaired binaural hearing after stroke. To address this, longitudinal measurements across the different phases of stroke are needed. One problem with research in clinical settings is that there is often insufficient time for extensive experimental procedures. Therefore, it is important to keep measurements as short as possible. Model-based experiment steering algorithms may be a solution to this problem.

This thesis aims to relate the underlying individual parameters to differences in performance in binaural hearing tasks (see Figure 1). The thesis consists of two projects investigating the individual impairments in binaural hearing in stroke patients and one project on the further development and application of a measurement procedure to assess the causes of individual impairments in the most time-efficient way.

The presented results provide insights into the relationship between pathology and binaural perception and the underlying processes. Thus, they contribute to closing the knowledge gaps described above. The thesis also provides an optimized time-efficient model-based experimental steering algorithm which is mainly useful in settings with restricted measurement time, such as clinics. This interdisciplinary work expands knowledge in the fields of neuroscience, audiology, and experimental design optimization.

Zusammenfassung

Der Hörsinn dient dazu, Schallquellen zu detektieren, zu identifizieren und zu lokalisieren. Die interauralen Unterschiede (d.h. Unterschiede zwischen den zwei Ohren) in Zeit und Pegel von eingehendem Schall können zur Lokalisierung von Schallquellen und zur Trennung auditorischer Objekte genutzt werden. Somit trägt das Gehör im Allgemeinen und speziell das binaurale Hören dazu bei, sich erfolgreich in der Welt zurechtzufinden. Beim Menschen und anderen Säugetieren befindet sich die erste Stufe der Verarbeitung binauraler Informationen im Hirnstamm. Neben diesen Verarbeitungskernen im Hirnstamm sind viele weitere Strukturen der primären Hörbahn sowie Hirnareale außerhalb der primären Hörbahn an der räumlichen Wahrnehmung und der Verbesserung der Hörwahrnehmung beteiligt. Pathologische Veränderungen in einer dieser Stufen können zu Schwierigkeiten bei binauralen Höraufgaben führen, doch die Forschung über die individuellen Folgen solcher Pathologien ist noch nicht abgeschlossen. Die Untersuchung der Hörfähigkeiten klinischer Populationen ist wichtig, um diesen eine effektive Diagnose und individualisierte Rehabilitation zu ermöglichen. Betroffenen Personen kann am besten geholfen werden, wenn sowohl die Auswirkungen als auch die zugrundeliegenden Pathologien eingehend verstanden sind.

Der ischämische Schlaganfall ist eine weit verbreitete Erkrankung, bei der der Blutfluss im Gehirn durch eine akute Verstopfung der Blutgefäße unterbrochen wird. In der Folge werden bestimmte Hirnareale nicht mehr mit Sauerstoff und Nährstoffen versorgt. Dies kann zu verschiedenen Symptomen führen, wie z. B. zu motorischen Defiziten, kognitivem Abbau und sensorischen Beeinträchtigungen. In mehreren Studien wurden bereits negative Auswirkungen von Schlaganfallläsionen auf die binaurale Wahrnehmung aufgezeigt. Die meisten dieser Studien wurden in der chronischen Phase des Schlaganfalls durchgeführt und schlossen nur Patient:innen mit einer Läsion in einem bestimmten Hirnareal ein. Jedoch würden eben solche Experimente unter Einbeziehung einer Vielzahl von Läsionsstellen in der akuten Phase Einblicke in die zugrundeliegende Enkodierung und Dekodierung binauraler Informationen ermöglichen. Darüber hinaus gibt es keine Literatur über die Erholung des beeinträchtigten binauralen Hörvermögens nach einem Schlaganfall. Hierfür sind Längsschnittstudien über die verschiedenen Phasen des Schlaganfalls hinweg erforderlich. Ein häufiges Problem bei der Forschung im klinischen Umfeld ist, dass nicht genügend Zeit für umfangreiche experimentelle Verfahren zur Verfügung steht. Daher ist es wichtig, die Messungen so kurz wie möglich zu halten. Modellbasierte Algorithmen zur Versuchs-

steuerung könnten eine Lösungsmöglichkeit für dieses Problem darstellen.

Das Ziel dieser Arbeit ist es, die zugrundeliegenden individuellen Parameter zu identifizieren, die zu unterschiedlichen Ergebnissen bei binauralen Höraufgaben führen (siehe Abbildung 1). Die Dissertation besteht aus zwei Projekten zur Untersuchung der individuellen Beeinträchtigungen des binauralen Hörens bei Schlaganfallpatient:innen und einem Projekt zur Weiterentwicklung und Anwendung eines Messalgorithmus, um die Ursache individueller Beeinträchtigungen möglichst zeiteffizient zu erfassen. Die vorgestellten Ergebnisse geben Einblicke in den Zusammenhang von Pathologie und binauraler Wahrnehmung sowie in die zugrundeliegenden Prozesse. Damit tragen sie dazu bei, die oben beschriebenen Wissenslücken zu schließen. Die Arbeit liefert zudem einen optimierten zeiteffizienten modellbasierten experimentellen Steuerungsalgorithmus, der vor allem in Umgebungen mit begrenzter Messzeit, wie z.B. in Kliniken, nützlich sein kann. Diese interdisziplinäre Arbeit erweitert das Wissen in den Bereichen Neurowissenschaften, Audiologie und der Optimierung der Experimentalplanung.

Graphical Summary

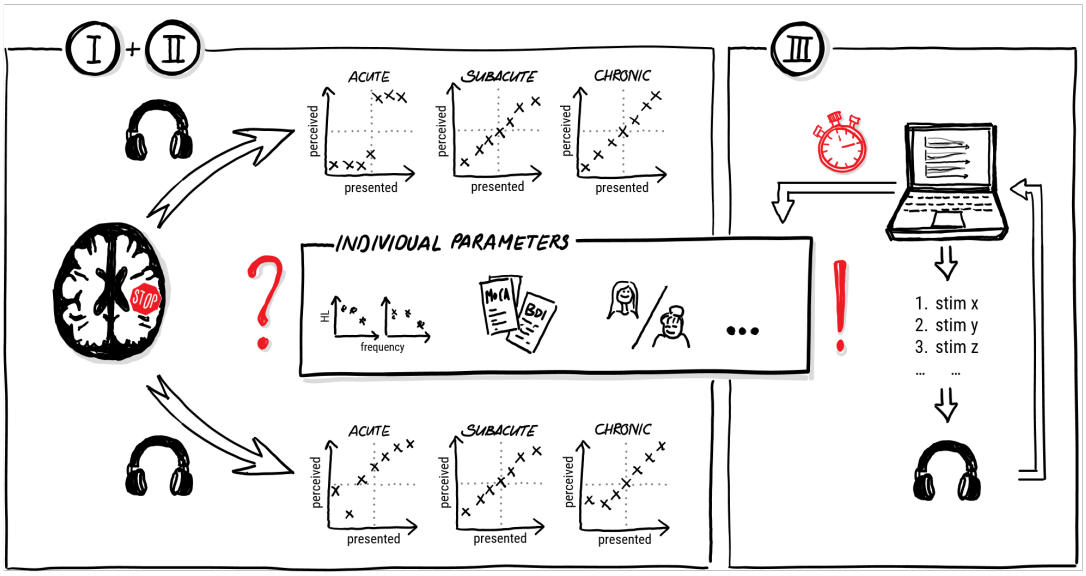

Figure 1: Graphical summary of the aims of this thesis

Contents

List of Abbreviations

ADC	Apparent Diffusion Coefficient
AN	Auditory Nerve
BDI	Beck's Depression Inventory
BMLD	Binaural Masking Level Difference
CAFPAs	Common Audiological Functional Parameters
CN	Cochlear Nucleus
DWI	Diffusion Weighted Imaging
FLAIR	Fluid-attenuated Inversion Recovery
IC	Inferior Colliculus
ILD	Interaural Level Difference
ITD	Interaural Time Difference
IPD	Interaural Phase Difference
LL	Lateral Lemniscus
LNTB	Lateral Nucleus of the Trapezoid Body
LSO	Lateral Superior Olive
MGN	Medial Geniculate Nucleus
MNTB	Medial Nucleus of the Trapezoid Body
MoBES	Model-based Experiment Steering
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MSO	Medial Superior Olive
MWT	Multiple-Choice Vocabulary Intelligence Test (Mehrfachwahl-Wortschatz-Intelligenztest)
NIHSS	National Institute of Health Stroke Scale
PAC	Primary Auditory Cortex
PTA	Pure Tone Average
SNR	Signal to Noise Ratio
SOC	Superior Olivary Complex
SRM	Spatial Release from Masking

1 | General Introduction

Hearing in general, and binaural hearing (i.e., the combination of information from the two ears) in particular, contribute to navigating the world successfully (for a review see Grothe et al., 2010). For instance, sound sources can be localized by integrating the information from the two ears, and the segregation of sound sources is easier when their spatial position, and hence the sound reaching the two ears, is different. The possibilities offered by binaural hearing are well studied, but the consequences of pathologies on binaural perception are still inconclusive (e.g., Litovsky et al., 2021). One such pathology that can influence binaural hearing is the highly prevalent disease of stroke (reviewed by Häusler & Levine, 2000). Experiments in the acute phase allow conclusions to be drawn about the underlying encoding and decoding of binaural information. This is because the acute disruption can hardly be compensated for by recovery processes up to that point. Thus, studies in the acute phase provide insight into the functionality of the damaged structure. However, most studies on the effects of stroke lesions on binaural hearing abilities have been conducted in the chronic phase of stroke. Furthermore, there is a lack of literature on the recovery of impaired binaural hearing after stroke. Both of these knowledge gaps are addressed in this thesis. Working with stroke patients has highlighted the importance of optimized measurements in situations in which measurement time is limited. One solution to this challenge is presented in this thesis in the form of a model-based experiment steering algorithm that enables efficient characterization of individual impairments. In summary, this thesis explores the relationship between pathology and binaural perception and presents a measurement algorithm for time-efficient diagnostics (see the graphical summary, Figure 1).

The basics of binaural hearing, including its relevance, the underlying physical properties, and the auditory processing stages are introduced in Section 1.1. The consequences of stroke on binaural perception and its recovery are discussed in Section 1.2. These sections are followed by an overview of the possibilities and difficulties of measurements in clinical settings regarding data collection and analysis, ending with the need for efficient auditory diagnostics (Section 1.3). The first chapter concludes with an interim summary (Section 1.4) and the aims of this thesis in Section 1.5. Chapters 2, 3, and 4 contain research articles: The effects of acute ischemic stroke on binaural perception are presented in Chapter 2. Observations of the longitudinal effects of ischemic stroke on binaural perception are provided in Chapter 3. Chapter 4 features an algorithm for model-based experiment steering. The three articles are followed in

Chapter 5 by a general discussion of their main findings (Section5.1), their implications (Section 5.2), and methodological considerations (Section5.3). Sections 5.4 and 5.5 provide prospects for the future and a conclusion to complete the thesis.

1.1 Binaural Hearing

The sense of hearing, known as audition, allows us to detect, identify, and localize sound sources even with our eyes closed and is, therefore, a vivid part of our conscious lives (Bear et al., 2016). Binaural hearing enables spatial awareness and enhances auditory perception. However, in contrast to the visual or somatosensory system, no explicit representation of space on the receptor surface is available to analyze the spatial origin of inputs. Instead, a spatial auditory representation has to be computed from the converging input of left and right ear (e.g., Grothe et al., 2010).

To be able to follow the subsequent content, it is necessary to have a basic understanding of binaural hearing, i.e., the combination of information from the two ears and its further processing. Section 1.1.1 outlines the relevance of binaural hearing. Then, in Section 1.1.2, insights are given into the physical properties of sounds employed for binaural hearing. Binaural information is processed in several stages from the ear up to the cerebral areas of the brain. The physiological basis of binaural hearing in mammals is discussed in Section 1.1.3.

1.1.1 Relevance of Binaural Hearing

The localization of sound sources is the most obvious use case for binaural hearing. Humans (and other species) can localize the position of sound sources within only a few degrees in accuracy in the horizontal and vertical dimensions. The accuracy of the localization depends on the position of the sound source, with the highest precision in front of the listener (e.g., Makous & Middlebrooks, 1990; Stevens & Newman, 1936). Localization performance also depends on the frequency content of the sound (e.g., Stevens & Newman, 1936; Yost et al., 2013). The smallest perceivable difference in sound source position, the minimal audible angle, is about 1° in front of the listener (Mills, 1958). Since we are usually not surrounded by static sound sources and tend to move, the more ecologically valid measure might be the just noticeable difference in the spatial location of moving sound sources. This minimal audible movement angle is with about $1.5-2°$ in front of the listener approximately twice as large as for static sound sources (Harris & Sergeant, 1971).

Besides the apparent advantages in spatial orientation provided by sound source localization, binaural hearing is involved more implicitly in the processing of listening

situations with multiple sound sources by segregating the incoming sound into distinct auditory objects. The detection of sounds in noise is facilitated in situations where their interaural differences deviate (interaural differences are described in more detail in Section 1.1.2). The detectability of such stimuli is likely to be correlated with the fluctuations in interaural phase and level differences. Functions for calculating these stimulus statistics are presented in Encke and Dietz (2022b). This beneficial effect over situations without interaural differences, referred to as binaural masking level difference (BMLD), has been demonstrated first by Hirsh (1948). The BMLD is maximal for the detection of an antiphasic tone (S_π) in in-phase noise (N_0).The magnitude of the BMLD varies with tone frequency (Hirsh & Burgeat, 1958), noise delay (Langford & Jeffress, 1964), interaural correlation of tone and noise (Robinson & Jeffress, 1963), and the interaural phase of tone and noise (Rabiner et al., 1966). The BMLD can be used to measure binaural hearing performance implicitly under highly controlled laboratory conditions. Of course, such an arrangement does not occur in everyday listening situations. Nevertheless, spatial release from masking (SRM), i.e., the benefit of speech detection with spatially separated sound sources, relies partially on binaural unmasking. Binaural unmasking is therefore critical for communication. It has been shown that the maximal benefit occurs for arrangements where the speaker is located in front and the noise left or right of the listener with maxima at around $+60^\circ$ and -60°. This is because improvements in the signal-to-noise ratio at one ear (better-ear listening) can be employed in addition to binaural unmasking (Culling & Lavandier, 2021, reviewed by). SRM has also been shown to be influenced by working memory capacity (Charney & Srinivasan, 2020) and age (Gallun et al., 2013).

To summarize, binaural hearing is used by a broad range of species (predators and prey alike) to navigate the world (see for a review Grothe et al., 2010). It is also beneficial in communicative scenarios, such as listening to a speaker despite background noise (Culling & Lavandier, 2021, see for a review). Consequently, binaural hearing is highly relevant to everyday life (Avan et al., 2015) and of clinical importance (Diedesch et al., 2021), which explains the need to understand and diagnose the causes of binaural perceptual impairments in individuals.

1.1.2 Physical Properties Used for Binaural Hearing

There are several physical properties of sound arriving at the inner ears that contain information about the location of the corresponding sound source. Spectral analysis (a comparison of sound energy across different sound bands) yields information about the elevation, i.e., the vertical location of sound sources (Blauert, 1969). This can be accomplished with one ear, in other words, monaurally. Monaural processing is not discussed here, since the focus is on the two binaural cues illustrated in Figure 2. A

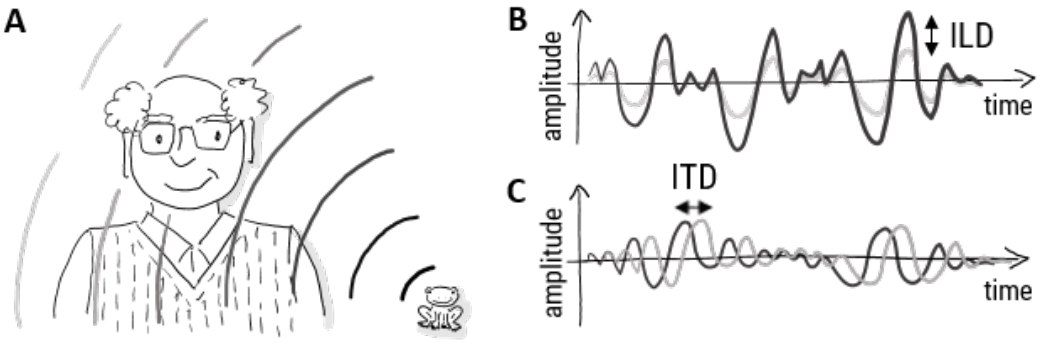

Figure 2: Simplified representation of the interaural level difference (ILD, panels **A** and **B**) and the interaural time difference (ITD, panels **A** and **C**)

comparison of the level and the time of arrival of the sound at the two ears can inform about the azimuth, i.e., the horizontal location of a sound source (Strutt, 1907). These computations are mainly performed within narrow-band sound-frequency channels, but may also involve information from adjacent frequency channels (Dreyer & Delgutte, 2006; Eurich et al., 2022; Klug et al., 2020).

The first of the two binaural cues is the interaural level difference (ILD, also known as interaural intensity difference, IID). As shown in Figure 2 A and B, it results from the shadowing effect of the head itself, which leads to a lower sound level at the ear further away from the sound source for high-frequency sounds (Blauert, 1997). For low-frequency sounds (with wavelengths longer than the diameter of the head) this effect is negligible for far-field sound sources (Strutt, 1907), whereas sound sources close to the listener's ear can evoke large ILDs (Brungart & Rabinowitz, 1999). In general, ILD depends on the frequency of the sound and the angular position of the sound source. Progressively higher ILDs are experienced when moving the sound source from the front to the side and with increasing sound frequency with a maximum of about 20-30 dB (Feddersen et al., 1957; Kayser et al., 2009).

For low-frequency sounds, listeners usually rely on the second of the binaural cues, the interaural time difference, or ITD for short (Macpherson & Middlebrooks, 2002; Strutt, 1907). The ITD is shown in Figure 2 A and C. It depends on the position of the sound source and the size of the listener's head: Adult humans experience maximal ITDs of $\pm 600 - 700\,\mu s$ for sound sources that are presented at 90° azimuth (Blauert, 1997). This limit is referred to as the "physiological range". For azimuthal angles farther from 90°, the magnitude of the ITD decreases.

The term "localization" refers to the spatial perception of a sound source in the extrapersonal space experienced in everyday listening situations with coherent ILD, ITD,

and monaural cues. On the contrary, "lateralization" refers to the left-to-right position of an intracranial perception of a sound source usually experienced when ILD, ITD, and monaural cues are not matched. A presentation of stimuli via headphones allows independent manipulation and presentation of ILD and ITD. In contrast to localization tasks, where interaural cues are in congruence and accompanied by monaural information, conclusions on the processing abilities of the individual cues can be drawn from lateralization experiments.

1.1.3 Physiology of Binaural Hearing

The mammalian auditory system can be split into two parts: The auditory periphery and central auditory stages (for comprehensive summaries see e.g., Moore, 2012; Plack, 2018; Tremblay & Burkard, 2012, Chapter 14). Since this thesis mainly focuses on altered binaural hearing caused by pathologies in the central auditory system, the auditory periphery is only presented shortly and the central auditory stages are covered in more detail.

Auditory Periphery

The auditory periphery consists of the external or outer ear, the middle ear, and the cochlea in the inner ear. Sound waves in the air enter the auditory system via the ear canal and reach the tympanic membrane. Vibrations of the tympanic membrane are forwarded via the middle ear ossicles to the cochlea. Bone-conducted sound is passed on to the inner ear via vibrations of the skull. In both cases, this motion is then transmitted to the perilymphatic fluid in the cochlea and leads to motion of the basilar membrane. The organ of Corti, which contains the sensory epithelium of the auditory system, including outer and inner hair cells, is located on this membrane. The outer hair cells mechanically amplify the motion of the basilar membrane. Displacement of the basilar membrane causes deflections of the cilia of the hair cells. Bending the cilia of the inner hair cells causes depolarization of the receptor potential of the inner hair cells by opening the ion channels. Through this process, the mechanically conducted sound is transformed into neural activity in the spiral ganglion neurons of the auditory nerve (AN), whose dendrites form large afferent synapses at the basis of the inner hair cells. The timing of the action potentials is phase-locked to the fine structure of sounds with a lower frequency (up to a few kHz) and to the envelope for amplitude-modulated high-frequency sounds (Grothe et al., 2010).

Pathologies can occur at each of these stages and influence hearing performance differently depending on the affected structure. Pathological changes to the outer and middle ear lead to conductive hearing loss, whereas pathologies of the cochlea result

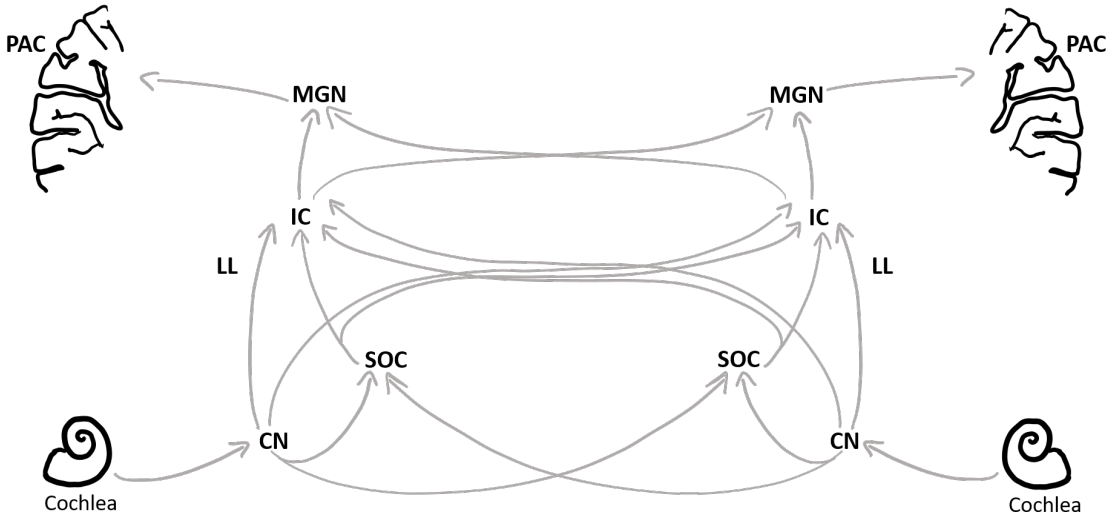

Figure 3: Schematic overview of the primary auditory pathway with the cochlear nucleus (CN), the superior olivary complex (SOC), the lateral lemniscus (LL), the inferior colliculus (IC), the medial geniculate nucleus (MGN), and the primary auditory cortex (PAC).

in so-called sensorineural hearing loss. The auditory nerve projects to central auditory stages, therefore impaired peripheral parts of the auditory system may cause altered inputs to central auditory processing stages.

Central Auditory Stages

Information conveyed by the auditory nerve enters the central nervous system at the pontomedullary junction via the vestibulocochlear nerve (eighth cranial nerve). The following overview only contains the main ascending pathway, referred to as the primary auditory pathway, depicted in Figure 3. Nevertheless, it is important to keep in mind that descending connections in the auditory system are critical for shaping sensory processing (Town & Bizley, 2021, for details read).

The first stage of the auditory pathway is the cochlear nucleus (CN). From its ventral part, projections reach the superior olivary complex (SOC) on both sides of the midline at the level of the pons. The SOC consists of the medial and lateral superior olives, the MSO and LSO, respectively. MSO and LSO are the first stages where information from the two ears is combined. The projections further proceed via the lateral lemniscus to the inferior colliculus (IC) at the caudal midbrain. Neurons of the dorsal CN project via the lateral lemniscus directly to the IC. The next processing stage after the IC is the medial geniculate nucleus (MGN), a nucleus in the thalamus, which is located in the rostral midbrain. From there, the primary auditory cortex (PAC) in Heschl's gyrus in the superior temporal gyrus, is reached.

The primary auditory cortex is the end point of the classical primary auditory pathway.

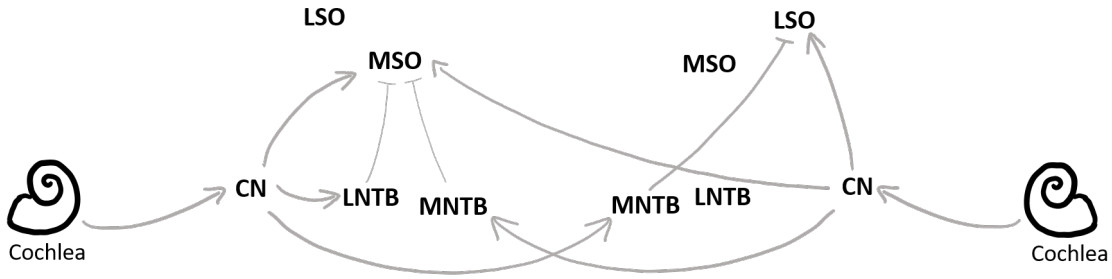

Figure 4: Schematic representation of the processing stage of binaural interaction at the brainstem level with the cochlear nucleus (CN), the lateral and medial nucleus of the trapezoid body (LNTB and MNTB), and the lateral and medial superior olive (LSO and MSO). Excitatory inputs are depicted with pointed, and inhibitory inputs with flat arrowheads.

However, auditory information is processed and represented in a variety of cerebral cortical areas: In addition to the primary auditory cortex (core), also the secondary (belt) and tertiary (parabelt) areas of the auditory cortex are involved in auditory perception. Information is processed in the six layers of the auditory cortex: Layers III and IV receive inputs from the thalamus (MGN), which are combined with inputs from other cortical fields in layers I and II. Layers V and VI are the major output stages of the auditory cortex. Neurons within these layers project to other cerebral cortical areas, thalamus, midbrain, and striatum (Hackett, 2015).

Since the information from the two ears travels bilaterally to higher stages, lesions above the level of the CN do usually not lead to serious deficits in simple hearing tasks (Häusler & Levine, 2000).

Binaural Processing Stages

As mentioned in Section 1.1.3 and shown in Figure 4, the SOC is the first stage where information from the two ears converges. The MSO mainly receives excitatory inputs from the CNs of the two sides (Cant & Casseday, 1986; Stotler, 1953) and has been found to encode fine structure ITDs (Remme et al., 2014). The LSO receives excitatory inputs from the ipsilateral side, but the input from the contralateral side is converted to inhibitory input by the MNTB (Cant & Casseday, 1986; Spangler et al., 1985; Stotler, 1953). This arrangement has been shown to encode the delays between fluctuations in the amplitude of sound at each ear (i.e., envelope ITDs) and ILDs (Remme et al., 2014).

The phase locking of neural activity of the bushy cells, which project to the SOC, is temporally even more precise than in the AN (Joris et al., 1994). This precise timing

of action potentials in the AN is of utmost importance for the processing of binaural information. Stimuli with ITDs that differ by only 10-20 μs have been demonstrated to be distinguishable by trained human listeners (e.g., Brughera et al., 2013; Thavam & Dietz, 2019). Even the maximum ITD within the physiological range (600-700 μs) is substantially shorter than the duration of one action potential (about 1000 μs). Therefore, spatial information can only be encoded by comparing the precisely timed phase-locked neuronal firing from the two sides. The just noticeable difference in ILDs is approximately 1 dB over a wide range of frequencies (Mills, 1960). Distortions of the precisely timed inputs to the SOC have been shown to cause deficits in the processing of ILDs and ITDs (Brand et al., 2002; Myoga et al., 2014).

There is a heated debate about the exact processing mechanisms that enable this remarkable binaural performance. The processing of binaural cues differs across vertebrates, because their tympanic ears independently evolved in the Triassic, about 210-230 million years ago (Grothe et al., 2010). It is therefore not surprising that the classical idea of encoding of ITDs and ILDs along an array of neurons with different axonal delays (Jeffress, 1948) does not seem to hold in all vertebrates: Such an arrangement of neuronal delay lines has been found in birds, but not in mammals, for example (Grothe et al., 2010). Instead, in different mammalian species, broadly tuned neurons with best ITDs outside the physiological range were found in both hemispheres (e.g., Brand et al., 2002; McAlpine et al., 2001). So-called opponent-channel models, in which information encoded in the two hemispheres is compared, can account for a large amount of data (Encke & Dietz, 2022a; Eurich et al., 2022; Klug et al., 2020).

The understanding of the neural processing of binaural cues after the SOC, and especially beyond the primary auditory cortex, remains limited yet (Town & Bizley, 2021). It is widely accepted that a complex network including prefrontal, frontal, parietal, and temporal areas contributes to human auditory space perception (e.g., Clarke et al., 2002; Griffiths et al., 1997; Lewald et al., 2008; Pavani et al., 2001).

It has been shown that spatial receptive fields in the PAC are typically tuned to sounds in the contralateral hemifield with only a few neurons tuned to the ipsilateral hemifield or the midline (Harrington et al., 2008). Interestingly, spatial tuning is sharpened by active engagement in localization tasks (Lee & Middlebrooks, 2011), reflecting the highly dynamic adaptive nature of cortical processing. Even with sharpening by the respective task, the spatial tuning of these cortical neurons is too broad to encode spatial position within a single neuron. ITDs outside the physiological range have been shown to elicit higher activity in the ipsilateral hemisphere, in contrast to balanced or higher activity on the contralateral hemisphere for ITDs that are usually experi-

enced under natural listening conditions (Thompson et al., 2006; von Kriegstein et al., 2008).

In other modalities, cortical maps with a topographic representation exist, but Middlebrooks (2021) concluded from 40 years of research on topographical representations of auditory space in the cortex, that such an auditory spatial map does not exist. It is still disputed how the cortical coding of auditory space is realized. In the case of opponent-channel processing, information of two neurons or two populations of neurons (residing in the two hemispheres) is compared. Another idea is distributed processing, where information is represented as patterns of activity across multiple neurons. These patterns could span one or both hemispheres (e.g., Day & Delgutte, 2013; Salminen et al., 2009).

The identification of brain areas that are involved in binaural hearing has mainly been achieved by studying localization abilities in animal models or human patients with brain damage. Probably the first structured investigations on the topic are those by Greene (1929) and Walsh (1957), who reported localization difficulties in patients with brain lesions, such as stroke. A selection of measurements of binaural processing impairments with stroke patients is given in Section 1.2.1.

1.2 Ischemic Stroke

In Germany, 1.6% of the adult population suffered a stroke or chronic consequences of a stroke during the past 12 months, resulting in stroke being one of the leading causes of disability (Robert Koch-Institut, 2017). Globally, stroke is even the second leading cause of death (World Health Organization, 2020).

Ischemic stroke is a medical condition in which the blood flow through the brain is disrupted by an acute blockage of blood vessels. Such a blockage can result in various symptoms, depending on which brain regions are supplied with oxygen and nutrients by the respective blood vessels. In hemorrhagic stroke, bleeding damages brain tissue and can thereby cause similar impairments.

The most commonly known symptoms of stroke are motor deficits, cognitive decline, and sensory impairments, as reflected in the BEFAST scale (noticeable problems associated with balance, eyes, face, arm, speech, and time) that is used to identify stroke (Chen et al., 2021). Usually, stroke lesions do not affect hearing thresholds, but it has been shown that binaural hearing abilities can be affected (reviewed by Häusler & Levine, 2000). Some stroke patients reported difficulties in sound localization in the chronic phase of stroke (Bamiou et al., 2012), whereas others are not aware of their binaural hearing impairment (e.g., Javer & Schwarz, 1995).

The phases of stroke recovery are the acute, subacute, and chronic phases of stroke. In this thesis, the designation of the three phases follows the recommendations of Bernhardt et al. (2017): The acute phase spans the first seven days, whereas the subacute phase spans the time of seven days to six months after stroke onset. Thereafter, the patients are in the chronic phase of stroke. The central nervous system can react with compensatory mechanisms and a reorganization in the form of adaptive or maladaptive neuroplasticity to altered inputs (Cramer et al., 2011). Recovery of impaired function is typically observed within the acute and subacute phases of stroke and only minor recovery is observed in the chronic phase (e.g., Lee et al., 2015; Skilbeck et al., 1983).

A brief review of the consequences of stroke regarding binaural hearing is given in the following Section (1.2.1). In Section 1.2.2, the recovery of binaural perception is discussed.

1.2.1 Binaural Hearing After Stroke

Stroke rarely affects simple hearing tasks (Häusler & Levine, 2000). An exception constitutes difficulties with speech stimuli, which are often observed after left-hemispheric lesions. The fact that strokes rarely affect auditory tasks is due to the multiple sources of blood supply of many central auditory structures and due to the redundancy of auditory information provided by the bilateral structure and hemispheric crossings above the SOC (Häusler & Levine, 2000).

Yet, binaural hearing has been reported to be impaired with unilateral lesions already at the beginning of the last century: Greene (1929) tested localization performance in the free field and isolated ILD and ITD perception of neurologic patients using a so-called "binaural stethoscope". He observed that some patients had difficulties in the ITD or ILD task, despite normal performance in the localization task. Admittedly, the methodology differed from nowadays standards, but he laid the foundation for studying binaural perception in clinical populations. Sanchez-Longo and Forster (1958) proposed a localization task to identify lesions in the right temporal cortex, because patients with such lesions showed difficulties in localization of sound sources in the left hemisphere. While some patients with basal ganglia lesions showed difficulties in tasks related to ITD-based lateralization, but not in localization tasks, other patients with cortical lesions had the opposite profile (Bellmann et al., 2001). The authors followed from these results that basal ganglia are involved in the allocation of spatial attention, whereas distortions of spatial representation were found in patients with cerebral lesions. Another distinction is the "implicit vs. explicit" use of binaural information. Thiran and Clarke (2003) reported a case of a patient with a right temporo-parieto-

frontal ischemic lesion who could use binaural cues implicitly for stream segregation, but not for explicit sound source lateralization. In a case study by Litovsky et al. (2002) difficulties in localization but not SRM were documented in a patient with a small lesion in the right dorsal midbrain, including the IC. Localization ability has been shown to be impaired by lesions of the right temporal lobe only, whereas discrimination tasks were affected by lesions of the left and right hemispheres (Zatorre & Penhune, 2001). Tissieres et al. (2019) followed from their experimental results that the implicit use of spatial cues in speech-related cues relies on a left-dominated network, although this might primarily reflect the dominance of left-hemispheric processing for speech stimuli. Using a lateralization task instead of a localization task, revealed that right temporal and parietal lobe lesions and right auditory pathway lesions cause impaired ILD-based lateralization (Bisiach et al., 1984) and ITD-based lateralization (Tanaka et al., 1999). One of the primary underlying pieces of work for the methods used in Chapters 2 and 3 of this thesis is the study by Aharonson et al. (1998) and Furst et al. (2000). They tested binaural hearing abilities in patients with stroke lesions in the brainstem (and multiple sclerosis patients) using a lateralization task. Their main finding was that binaural performance was affected in cases when lesions overlapped with the auditory pathway. More specifically, center-oriented lateralization was found with lesions of the caudal pons, whereas side-oriented lateralization was found in patients with lesions rostral to the SOC. Spierer et al. (2009) tested lateralization performance in patients with cortical lesions with the same methods as Aharonson et al. (1998). Mainly in accordance with the results of Sanchez-Longo and Forster (1958), Tanaka et al. (1999), and Zatorre and Penhune (2001), Spierer et al. (2009) found more frequent and more severe deficits in patients with right-sided lesions compared to left-sided lesions: Right-sided lesions influenced both, the perception on the contralesional as well as the ipsilesional side, whereas left-sided damage led to impairments in the contralesional hemifield. In summary, several studies have been conducted on the effects of stroke on binaural hearing. However, comparisons between them are difficult to make because they all used different methods and each studied specific lesion sites.

Auditory Neglect

Closely related to the inability to correctly localize or lateralize sounds in one hemifield after stroke is the phenomenon of neglect. Neglect manifests in "a failure to report, respond, or orient to stimuli that are presented contralateral to a brain lesion when this failure is not due to elementary sensory or motor disorders" and occurs in different modalities (Heilman et al., 2000). Impaired perception of auditory stimuli in one hemifield is called auditory neglect and is found more frequently after right-

hemispheric lesions compared to left-hemispheric lesions, especially when the temporal lobe is damaged (e.g., Gokhale et al., 2013; Guilbert et al., 2016; Heilman & Valenstein, 1979; Pavani et al., 2001; Tanaka et al., 1999; Zimmer et al., 2003). Auditory spatial neglect can therefore be regarded as a medical term for deficient binaural performance following a (right-hemispheric) stroke.

1.2.2 Recovery of Binaural Hearing

The recovery of binaural hearing with altered binaural inputs has been studied using various methods. In a study by Florentine (1976), normal-hearing participants wearing unilateral ear plugs were asked to alter the ILD of a stimulus so it was perceived on the midline. After only a few days, the initial localization bias caused by the altered binaural input approached the two types of biases observed in the long-term hearing-impaired group: Some participants adjusted the stimuli at the two ears to be equally loud to perceive them on the midline. For others, the stimuli had to be equally intense to be perceived on the midline. The localization bias that was caused by artificially introduced ITDs via electronic delay lines has been shown to be reduced by about 50% after a few days (Javer & Schwarz, 1995). Another method to alter ITD and ILD cues was employed by Feinstein (1973). They conducted experiments underwater, in which the higher speed of sound and a reduced head-shadow effect resulted in smaller binaural cues. In line with the other studies on the topic, adaptation to altered binaural cues was observed within hours to days as reviewed by Wright and Zhang (2006). Besides the observation of behavioral changes to altered binaural inputs, Trapeau and Schönwiesner (2015) showed that there are changes in the hemispheric lateralization of auditory cortex activity. Importantly, re-learning of acoustic features seems not to generalize to non-trained stimuli but is restricted to specific acoustic features (Butler, 1987; Keuroghlian & Knudsen, 2007). Butler (1987) showed that it is possible to learn to rely more on monaural spectral cues when no informative binaural input is available anymore. In general, specific training leads to faster adaptation to altered spatial cues than mere exposure does (Mendonça, 2014).

There is no literature on the ability to recover from binaural hearing impairments after stroke. Most studies have been conducted in the chronic phase of stroke (see Section 1.2.1). To my knowledge, there has never been a longitudinal study of binaural hearing abilities in stroke patients. Nevertheless, there is evidence that binaural performance can recover within the acute and subacute phases of stroke: First, full or partial adaptation to altered binaural cues has been demonstrated in neurologically healthy participants in many studies. Second, there are many reports of general functional recovery following stroke.

Studying localization difficulties in bimodal cochlear implant users (i.e., cochlear implant on one ear and a hearing aid on the other ear) revealed that the auditory system cannot compensate for the mismatch in processing times of the two devices, but strong improvements in localization abilities can be achieved by a technical latency compensation (Angermeier et al., 2023). In analogy to this great success, gaining insight into the individual nature of binaural processing difficulties in stroke patients might allow to provide some kind of technical compensation algorithms for these patients, as suggested by Brown (2018).

1.3 Measurements in Clinical Settings

As summarized by Meyer et al. (2022), conducting research in clinical settings is challenging for several reasons: Competing demands, research not being a priority for the organization, a lack of opportunity and support, and difficulties associated with the clinicians' knowledge, confidence, and beliefs were the main reasons named by hearing care professionals. However, lack of time is the most frequently named barrier identified in several studies (Meyer et al., 2022). Also for non-research measurements in clinical settings, such as those frequently done for audiological diagnostics, measurement time is limited. Keeping measurements as short as possible also reduces the influence of unaccounted factors such as fatigue, attention, and motivation.

This section first gives insights into the issues encountered when doing research in clinical settings (see Section 1.3.1). Clinical research is as important as laboratory research because both provide insights and knowledge that cannot be obtained from the other. In Section 1.3.2, the connecting elements of clinical and laboratory research, namely data and models are discussed. Given that diagnostic processes are often very complex and measurement time is a precious resource in clinical routine, models can be employed for targeted diagnostics in less time. The section therefore concludes with the application of auditory models for diagnostics (Section 1.3.3) and for measurement steering (Section 1.3.4).

1.3.1 Advantages and Disadvantages in Clinical Settings

Arguably, the most crucial aspect of research in clinical settings is the chosen population. In contrast to basic psychoacoustic experiments, which are often conducted with students, measurements in clinical settings involve patients with medical conditions. This can have a disadvantageous impact on scientific studies. Whenever the population under investigation is not young and healthy, additional factors are to be expected that influence the results of the experiments: Oftentimes, pathologies like conductive or sensorineural hearing loss are accompanied by commodities (reviewed

by Besser et al., 2018). One of the most prevalent confounding factors in studies within the medical context is age (see for example a meta-analysis on the effects of age and hearing loss on sensitivity to temporal fine structure: Füllgrabe & Moore, 2018). Moreover, motivation, cognitive abilities, and emotional status influence results as those presented in Chapters 2 and 3. As summarized by Gallun (2021), "there are substantial challenges associated with analyzing 'nature's experiments'. The most difficult obstacle is that, unlike in the laboratory, the perturbations of the system are not uniform and are not easily documented".

On the other hand, studying clinical populations also has advantages: Oftentimes, a high number of participants can be recruited with less effort than outside the clinics. Data collected in the course of clinical routines can be used to obtain a comprehensive picture of individuals. This requires the combination of data from different disciplines, such as data on the severity of stroke symptoms provided by neurologists, magnetic resonance imaging (MRI) data gathered by radiologists, and psychoacoustic data, collected by auditory scientists. Interdisciplinary research enables to focus on individual patients with all confounding influences case by case and the obtained results go beyond those of the individual disciplines.

1.3.2 From Data to Models and Vice Versa

Even though obstacles exist for research in clinical settings (see Section 1.3.1), the results are valuable both for basic research and for individual patients. In the best case, a combination of the two is given: Studies such as the ones presented in Chapters 2 and 3 of this thesis, provide information about the individual impairments of the participants. The results can be of relevance for the individual for (a) gaining an understanding of specific difficulties, (b) being a starting point for rehabilitation, or (c) being the data basis underlying assistive devices or aiding algorithms. In addition, the gained knowledge can be used to develop comprehensive models. Models are simplified representations of systems and a model of the binaural system usually involves multiple non-linear stages to represent encoding and decoding of binaural information. Less complex models with no or fewer non-linear stages, such as the one presented by Eurich et al. (2022), can account for behavioral data well, but the goal of auditory diagnostics demands more physiologically-inspired model architectures. To be able to represent not only young and healthy but also hearing-impaired listeners, the model parameters need to reflect individual pathologies.

A comprehensive model including all stages of the binaural system does not exist so far (see Section 1.3.3). As soon as it is developed, it could be used for model-based diagnostics. An algorithm that allows to steer experiments based on a model is presented

in Chapter 4. This approach allows to start with a model and to end up with estimations of the model parameters that represent the individual internal (pathological) parameters of a patient. As long as no complete model does exist, two tasks remain in parallel: (1) collecting data in different populations using diverse tasks, and (2) developing or improving algorithms that can be used later on in clinical settings to ease data collection, individualized diagnostics, and the quality of collected data.

1.3.3 Model-based Audiological Diagnostics

Computer models of the auditory system have already been employed to assist diagnostics. For instance, Panda et al. (2014) simulated data of a psychoacoustic test battery using a physiologically-inspired model by Meddis (2006). By varying one parameter at a time, they were able to make suggestions on the underlying pathologies. Along the same lines also Sackmann et al. (2019) identified various pathologies based on a finite element model of the human ear. Physiological models as those presented by Sackmann et al. (2019) or Verhulst et al. (2018) are based on a high number of model parameters. Consequently, the amount of data that is necessary when using these models for audiological diagnostics quickly increases from a few minutes of measurement time to collect enough data to estimate a single parameter (e.g., Brand et al., 2002) to hours for the prediction of three parameters (e.g., Herrmann & Dietz, 2021). Owing to the high redundancy and many efferent regulations in the highly nonlinear auditory system, ambiguities in the prediction of internal parameters may occur, as discussed in Klug et al. (2020), for example.

Functional models are usually based on fewer, though more abstract parameters. Plomp (1978), for instance, proposed a model based on a distortion component and an attenuation component. These two parameters, which characterize a listener's hearing impairment, can help to predict the possible effects of specific hearing-aid settings. A profiling of hearing-impaired listeners to identify possible aiding mechanisms has also been suggested by Buhl et al. (2019) and Sanchez Lopez et al. (2018) was able to identify the most informative measurements for auditory profiling and characterization of individual hearing loss.

1.3.4 Model-based Experiment Steering

The goal of audiological diagnostics is to identify the causes of a person's hearing impairment. There is a broad range of measurement techniques to investigate different aspects and pathologies of the auditory system (reviewed by Hoth & Baljic, 2017). Since the same behavioral outcome can be caused by a variety of pathologies and their combinations, rarely a single test is conclusive, more often a combination of sev-

eral tests is necessary to differentiate between pathologies. It is not known during the measurements which exact conditions are those that will be relevant for refining the diagnosis. Consequently, if not enough time is spent on measuring all possible conditions several times, the obtained data might not allow accurate parameter estimation later on. The most efficient measurements are therefore those that measure only the conditions needed for the optimization process. As summarized in Section 1.3.3, a variety of models have been suggested to aid auditory diagnostics, but these models require data to be collected first and then analyzed.

Herrmann and Dietz (2021) developed a likelihood-based procedure running in parallel to the measurements that addresses the above-mentioned issues: Using this procedure, only those conditions are measured that add information to refine (diagnostically relevant) model parameter estimation. Thus, the procedure constitutes a useful tool for time-efficient, targeted diagnostics. The outcome is a quantitative description of an individual's internal parameters or pathology, such as an estimated loss of 20-30% of the inner hair cells. Such results could also serve as quantitative input for potential aiding algorithms. The procedure can theoretically be used with any model and experiment, but the approach has so far only been tested with an in-silico patient, i.e., a computer-simulated patient. In Chapter 4 of this thesis, the model-based experiment steering algorithm by Herrmann and Dietz (2021) is further developed and its applicability is tested on a group of young normal-hearing participants doing a tone-in-noise detection task.

1.4 Interim Summary

Due to the importance of binaural hearing in everyday life as described in Section 1.1.1, the high prevalence of stroke (see Section 1.2) and its previously demonstrated impact on binaural hearing discussed in Section 1.2.1, it is essential to gain a better understanding of the effects of stroke on binaural perception. Even though several studies on the effects of stroke lesions on binaural perception have been conducted, they were mainly done in the chronic phase of stroke and each study included only a lesion-location-based subgroup of the stroke population. The studies are either case studies describing individual impairments or present results pooled over a patient group. To get a full picture of the situation, it is necessary to describe individual effects in combination with group effects. None of the previous studies tested patients with different lesion locations on the same binaural listening tasks during the acute, subacute, and chronic phases of stroke. By studying stroke patients with different lesion locations and the longitudinal measurement design, the results presented in Chapter 2 and Chapter 3 of this thesis constitute a novel contribution to the existing body of

literature. Importantly, quantitative analyses both on a group and individual patient level are presented.

When working with clinical populations such as stroke patients, it is crucial to choose the right tests for the limited time available as discussed in Section 1.3. Chapter 4 presents the improvements and testing of a mode-based experiment steering algorithm that allows the characterization of individual binaural hearing abilities in terms of model parameters. In addition, the further development of a simple, yet accurate binaural hearing model is described.

1.5 Aims of the Thesis

The central objective of this thesis is to relate the underlying individual parameters to differences in performance in binaural hearing tasks (see Figure 1). To this end, stroke patients as well as young normal hearing subjects were assessed using psychoacoustic measurements.

The research contributes to existing knowledge in fields such as neuroscience, audiology, and experimental design optimization. It allows insights into the relationship between pathology and binaural perception and the underlying processes. In addition, knowledge is gained on optimized experimental steering, which is mainly of importance in settings with restricted measurement time, such as in clinics.

More specifically, the following research questions are addressed:

Project I:
What are the immediate effects of acute ischemic stroke on binaural perception?

Project II:
Does binaural perception change across the different phases of stroke recovery?

Project III:
Can an algorithm be used to steer experiments for more efficient measurements?

2 | Project I: What are the immediate effects of acute ischemic stroke on binaural perception?

This chapter includes the research article "Effects of acute ischemic stroke on binaural perception", which was published in 2022 in Frontiers in Neuroscience (https://doi.org/10.3389/fnins.2022.1022354).

The purpose of this study was to explore the individual binaural perception of patients in the acute phase of stroke with clinically mild stroke symptoms. Insight into the involvement of the lesioned structures in binaural processing are gained, since plasticity, compensatory mechanisms, or relearning are not expected shortly after stroke. The results of a lateralization task, a tone-in-noise detection task, cognitive assessments, depression screening, and audiometric testing were compared to those of an age-matched control group. The locations of the stroke lesions were obtained using magnetic resonance imaging acquired in the clinical standard routine. Various quantitative approaches were employed to compare the results both on a group level and individually. The study revealed binaural impairments in the majority of stroke patients. The performance in the lateralization task differed substantially from the control group in many patients, whereas the performance in the tone-in-noise detection task was not impaired.

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Contributions:
AD, MD, and PS contributed to the conception and design of the study. AD, MD, PS, and KW planned the experimental procedures. AD organized the database, performed the analysis, and wrote the first draft of the manuscript. MB and AM recruited participants and acquired data. AD, PS, and BS did MRI analyses. AD and MD interpreted the data. MD and HP wrote further sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Effects of acute ischemic stroke on binaural perception

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Stroke-induced lesions at different locations in the brain can affect various aspects of binaural hearing, including spatial perception. Previous studies found impairments in binaural hearing, especially in patients with temporal lobe tumors or lesions, but also resulting from lesions all along the auditory pathway from brainstem nuclei up to the auditory cortex. Currently, structural magnetic resonance imaging (MRI) is used in the clinical treatment routine of stroke patients. In combination with structural imaging, an analysis of binaural hearing enables a better understanding of hearing-related signaling pathways and of clinical disorders of binaural processing after a stroke. However, little data are currently available on binaural hearing in stroke patients, particularly for the acute phase of stroke. Here, we sought to address this gap in an exploratory study of patients in the acute phase of ischemic stroke. We conducted psychoacoustic measurements using two tasks of binaural hearing: binaural tone-in-noise detection, and lateralization of stimuli with interaural time- or level differences. The location of the stroke lesion was established by previously acquired MRI data. An additional general assessment included three-frequency audiometry, cognitive assessments, and depression screening. Fifty-five patients participated in the experiments, on average 5 days after their stroke onset. Patients whose lesions were in different locations were tested, including lesions in brainstem areas, basal ganglia, thalamus, temporal lobe, and other cortical and subcortical areas. Lateralization impairments were found in most patients with lesions within the auditory pathway. Lesioned areas at brainstem levels led to distortions of lateralization in both hemifields, thalamus lesions were correlated with a shift of the whole auditory space, whereas some cortical lesions predominantly affected the lateralization of stimuli contralateral to the lesion and resulted in more variable responses. Lateralization performance was also found to be affected by lesions of the right, but not the left, basal ganglia, as well as by lesions in non-auditory cortical areas. In general, altered lateralization was

common in the stroke group. In contrast, deficits in tone-in-noise detection were relatively scarce in our sample of lesion patients, although a significant number of patients with multiple lesion sites were not able to complete the task.

KEYWORDS

binaural hearing, psychoacoustics, brain lesions, lateralization, binaural masking level difference, magnetic resonance imaging, stroke

1. Introduction

The interaural level differences (ILD) and interaural time differences (ITD) provide the basis for localizing sound sources in the horizontal plane. This ability informs the listener about the spatial location of an approaching vehicle, for instance, but is also crucial for segregating different auditory streams in more complex listening environments, such as multiple talkers in a crowded restaurant. Especially the latter ability is clearly compromised in listeners with sensorineural hearing loss (e.g., Gatehouse, 2004; Shinn-Cunningham and Best, 2008). However, spatial hearing can also be impaired by damage to the central nervous system. The consequences of such damage for spatial hearing and binaural perception are arguably less well understood (Gallun, 2021).

One relatively prevalent type of central nervous system damage is stroke. For instance, the GEDA 2014/2015-EHIS study found that, in Germany, 1.6% of adults suffered a stroke or chronic consequences of a stroke during the past 12 months (Robert Koch-Institut, 2017). Central stroke lesions do not usually affect hearing thresholds, but they can affect binaural hearing (Häusler and Levine, 2000). This is also reflected in patient-reported difficulties in sound localization in the chronic phase after stroke, as shown in Bamiou et al. (2012). Given the relatively high prevalence of stroke in the general population, an improved understanding of its effects on spatial hearing would be desirable.

Previous studies have revealed deficits in binaural hearing in patients with different stroke lesion locations. Furst et al. (2000) investigated the binaural performance of patients with brainstem lesions using a test of interaural difference discrimination and with a lateralization task. Binaural performance was affected whenever the lesion overlapped the auditory pathway. Lesions of the caudal pons led to center-oriented lateralization, whereas lesions rostral to the superior olivary complex led to side-oriented lateralization results. Just-noticeable differences in ILD and ITD were affected in some patients with pontine lesions.

Comparable methods were used by Spierer et al. (2009), who studied the effects of cortical lesions on ITD- and ILD-based lateralization. The findings suggested a dominance of the right hemisphere in auditory spatial representation. More frequent and more severe deficits were observed after right-sided, compared to left-sided, damage. Lesions of the right hemisphere influenced contralesional as well as ipsilesional lateralization, whereas the effect of left-sided damage was restricted mainly to the contralesional hemifield.

Along the same lines, the effect of auditory neglect (impaired perception of auditory stimuli in one hemispace) is also more frequently observed for right-hemispheric lesions, especially when the temporal lobe is damaged (Gokhale et al., 2013). The term neglect is used for various impairments and different modalities (Heilman et al., 2000). As reviewed in Gokhale et al. (2013), language-related stimuli are mainly associated with the left temporal cortex, whereas non-language stimuli are predominantly processed in the right hemisphere. As a result, processing of non-language stimuli is often impaired, and in some cases, neglected after damage to the right hemisphere.

Two separate processing streams are suspected to be responsible for the 'where' and 'what' of auditory perception. This hypothesis is supported by the fact that binaural hearing performance of the centrally impaired auditory system depends not only on the location of the damaged area, but also on the task to be performed (Bellmann et al., 2001). For instance, a case report of a patient with lesions in the right hemisphere showed a difference between using binaural cues implicitly or explicitly (Thiran and Clarke, 2003). The patient was able to implicitly use binaural cues for stream segregation in a spatial-release-from-masking task, but had no explicit lateralized perception at all when presented with stimuli with ITDs. The implicit and explicit use of binaural cues was also investigated by Tissieres et al. (2019), with a larger number of participants. They concluded that the implicit use of auditory spatial cues relies on a distinct, left-dominated network.

In general, previous studies on the effect of lesions of the central nervous system on binaural perception were mainly investigated in the chronic phase of stroke in subgroups of stroke populations. Based on the results of, e.g., Trapeau and Schönwiesner (2015), who showed that relearning of localization with altered ITDs is possible within a few days, we assume that stroke-induced lateralization impairments will be strongest in the acute phase and at least partially recovered in the chronic phase of stroke. The existing studies revealed a plethora of deficits that vary significantly across lesion location, stimulus

material and patients. The great variability and individual nature of the findings indicate that further large-scale research is needed to move closer to a complete understanding of the effects of stroke on binaural hearing performance. By studying the disturbed system shortly after stroke onset, the patients' responses may give novel insights into the role of the affected areas in spatial hearing, including its relevance for the healthy system.

In addition to studies with stroke patients, neuroscientific experiments with healthy adults revealed different mechanisms of ITD processing along the auditory pathway. Thompson et al. (2006) presented large ITDs (±1500 μs), well outside the range of ITDs of ±700 μs, that are usually experienced under natural listening conditions. Using functional magnetic resonance imaging (MRI) neural activity was measured by means of the blood oxygenation level dependent response. For these large ITDs, they found higher neural activity in the ipsilateral, compared to the contralateral, side of the mid-brain, which is the opposite of findings for smaller ITDs. A related study by von Kriegstein et al. (2008) revealed that at the level of the cortex, both hemispheres were activated for these large ITDs. For the small ITDs, predominantly the primary auditory cortex in the contralateral hemisphere was active. These data show that coding of ITD in the cortex is fundamentally different from the mid-brain representation of ITD, but it remains unclear how such large ITDs are perceived if lesions impair the encoding or decoding at different stages of the auditory pathway.

Studying clinical populations has shaped our understanding of binaural processing, and is still useful to supplement studies in different animal models (Gallun, 2021). Currently, structural MRI is used in standard clinical routine for stroke patients. The combination of the information on the precise lesion location, and the patients' performance in behavioral tasks, could lead to insights into individual problems in binaural processing and possible ways to individualize therapies.

The detrimental effects of stroke lesions on binaural hearing tasks vary not only for different lesion locations and lesion sizes, but can also be shaped by factors such as age, conductive or sensorineural hearing loss, cognitive abilities, and other non-auditory characteristics. Therefore, in addition to group analyses that are compared to age-matched control subjects, focusing on individual patients with all their confounding influences case by case remains unavoidable.

The objective of the current exploratory study was to investigate the binaural perception of individuals in the acute phase of stroke, compared to an age-matched control group in a quantitative, yet individual manner. Since binaural deficits have been observed for lesions across multiple brain areas that are not directly related to audition, we did not limit our study to predefined regions of interest. This choice was further motivated by our aim to conduct a relatively large-scale study with potential to reveal patterns that would remain unnoticed or ambiguous with smaller patient cohorts. We conducted two binaural experiments using headphone stimulation. Performance in both experiments relied on using interaural differences. In the first experiment, a binaural tone-in-noise detection task, the implicit use of interaural cues was sufficient to detect differences to the reference stimulus. In the second experiment, a lateralization task, listeners had to explicitly use interaural cues to judge the perceived intracranial position of the stimulus. These experiments, and an additional general assessment, were completed by patients that had rather small lesions in different brain areas. The location of the lesion was established based on previously acquired MRI data.

2. Materials and methods

2.1 Participants

In total, 50 stroke patients (mean age of 63 years, SD: 14 years, 20 female, 30 male) and 12 control subjects (mean age of 61 years, SD: 14 years, 9 female, 3 male) participated after passing audiometric and cognitive assessments (see Sections "2.2 General assessment" and "2.4.1 Audiometry" for details) and providing written informed consent. Participants that had a stroke will be referred to as patients, whereas those participating in the control group will be referred to as control subjects. The study was approved by the Medical Research Ethics Board of the University of Oldenburg, Germany. The stroke patients were recruited in the stroke unit of the Evangelisches Krankenhaus, Oldenburg, Germany and tested in a quiet room. Only those patients participated who could understand and produce speech, who were mobile and in a general stable condition, and able to complete the different tasks despite their recent stroke. Exclusion criteria were additional neurological diseases or a pure-tone average of 40 dB HL or more (see Section "2.4.1 Audiometry"). The stroke patients participated in the experiments on average 5 days (range: 1—9 days, 16 days for one patient, SD: 2 days) after stroke onset. The symptoms of stroke, as measured by the National Institute of Health stroke scale (see Section "2.2 General assessment"), ranged from 0 to 6 points, except for one patient with a score of 20 points. The median of the scores was one point, thus representing a stroke cohort suffering from minor stroke. The control group was age-matched and followed the same exclusion criteria.

2.2 General assessment

Preceding the psychoacoustic experiments, the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) was used to screen for mild cognitive impairment or dementia. The test contains 30 tasks targeting different cognitive abilities, and is scored with a maximum of 30 points. Scores below 26 points suggest mild cognitive impairment. Three patients with

a performance score of 17 or lower were excluded from the subsequent experiments.

The National Institute of Health stroke score (National Institute of Neurological Disorders and Stroke [NIHSS], 2019) was obtained as part of the clinical routine 24 h after the patients came to the hospital. It consists of several measures judging the severity of the symptoms of stroke, with a maximum score of 42 points. Scores below 5 are classified as minor stroke, below 15 as moderate stroke, and above this as moderate to severe and severe stroke. The score includes several items related to motor functions, but no item explicitly targeting auditory impairments.

To quantitatively assess the intensity of possible depression, we used the short version of the Beck's Depression Inventory (BDI, Beck et al., 2013). It contains 7 sets of statements from which are chosen those that best describe the patient's current state. To be compatible with the full version, the results are scaled to fall within the ranges of the full test. Scores below 9 indicate no or minimal depression, those between 9 and 13 indicate mild depression. Moderate depression is indicated by scores between 20 and 28, and severe depression by scores in the range between 29 and 63.

The multiple-choice vocabulary intelligence test, the German MWT-B (Lehrl, 2005), was used as an estimator for the premorbid intelligence (unaffected by the stroke). It consists of 37 items, each containing five words. Only one of the five words is an established word that must be recognized, whereas the others are neologisms. The higher the number of correctly detected words, the higher the estimated crystallized intelligence (part of a person's intelligence that consists of knowledge that comes from prior learning and past experiences).

2.3 Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) was obtained as part of the clinical routine for all patients. Two different systems were used: a Siemens Magnetom Symphony (1.5 T) and a Magnetom Sola (1.5 T). Lesion location and lesion volume were extracted from these images based on the combined information of diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC) mapping, and the fluid-attenuated inversion recovery (FLAIR) sequence. All areas that were hyperintense in DWI (and had a low signal in the ADC map, thus representing restricted diffusion) were outlined on the FLAIR images using the visualization tool MRIcroGL (Rorden and Brett, 2000), and the volume of the lesions were calculated. The analyses of the images was done using FSL (Jenkinson et al., 2012), a library of analysis tools for FMRI, MRI and DTI brain imaging data. Brain extraction was carried out using FSL BET (Smith, 2002) based on the FLAIR images, since they allowed better extraction than the available T1-weighted images. The fractional intensity threshold for BET was chosen case by case, to obtain the best extraction. The MR images were obtained in the standard clinical routine. Thus, for a majority of patients, only 2D MR images were available. Only in some cases 3D T1 and/or 3D FLAIR data were acquired. Linear registration of the brain-extracted FLAIR images to MNI 152 space, a structural template, provided by the Montreal Neurological Institute, was carried out using FSL FLIRT (Jenkinson et al., 2002). The quality of the resulting images was visually controlled for every subject. The same transformations were applied to the lesion masks. The lesion location was then estimated based on the AICHA atlas (Joliot et al., 2015).

Overlap of the MNI-registered stroke lesions with brain areas that belong to the auditory pathway were estimated as follows: The main nuclei of the primary auditory pathway were defined by the mask provided by Sitek et al. (2019) for the subcortical areas. The auditory cortex was defined by the term-based meta-analyses for the term 'auditory cortex' on the website neurosynth.org (Yarkoni et al., 2011), which created a mask using data from 279 MRI studies.

2.4 Psychoacoustic measurements

For all of the psychoacoustic experiments, closed headphones with high passive sound attenuation (HDA300, Sennheiser electronic GmbH, Wedemark, Germany) and driven by an external soundcard (UR22mkII, Steinberg Media Technologies GmbH, Hamburg, Germany) were used. The stimuli were generated and reproduced by custom-made MATLAB scripts using the psychophysical measurement package AFC (Ewert, 2013). The sampling rate was 48 kHz.

2.4.1 Audiometry

Pure-tone audiometric testing for a restricted set of frequencies (500, 1000, and 3000 Hz) was conducted preceding the psychoacoustic experiments using a one-interval two-alternative forced-choice procedure controlled by the experimenter. The testing followed a one-up, one-down adaptive procedure. The tracks ended after eight reversals (initial step size was 20 dB, after the second reversal 10 dB, after the fourth reversal 5 dB) and the thresholds were computed from the mean of the last four reversals. The pure-tone average over the three measured frequencies was calculated for the left and right ear individually (PTA3 L and PTA3 R, respectively), and averaged over the two ears (PTA3). In addition, the absolute difference between the left and right PTA3 (PTA3 asymmetry) was calculated. Two patients with a PTA3 L and/or a PTA3 R of more than 40 dB HL were excluded, leading to a total of 50 patients for further study.

2.4.2 Tone-in-noise detection

In the tone-in-noise detection experiments, the participants were presented with three intervals containing 500-ms bursts of octave-wide white noise centered around 500 Hz (333–666 Hz).

The stimuli were gated with 20-ms raised cosine onset and offset ramps. The intervals were separated by 300-ms silent gaps. In one of the three intervals, an additional 500-Hz pure-tone of 420 ms duration was added and temporally centered in the noise. The tone had the same ramp parameters as the noise, but its onset was 40 ms later than the noise. Similarly, the tone offset was 40 ms before the noise offset. The participants' task was to detect the deviating interval (the one containing the tone) and to press key number '1,' '2,' or '3' on a computer keyboard, indicating whether the first, second, or third interval was the odd one. The tone was either interaurally in phase with the noise (condition N_0S_0), or had an interaural phase difference of π (condition N_0S_π). The experiment started without any training and with two runs of the N_0S_π condition. This was followed by one run of the N_0S_0 condition. The noise was presented with 60 dB sound-pressure level (SPL). The level of the tone was initially 65 dB SPL in the N_0S_0 condition and 50 dB SPL in the N_0S_π condition. The level varied according to a one-up, three-down procedure, with a step size of 4 dB up to the second reversal, and a step size of 2 dB for the remaining 8 reversals, converging to 79.4% correct thresholds. Thresholds are calculated as the average of the last 8 reversals. If the staircase track hit the maximum tone level of 80 dB SPL during a measurement, re-instructions on how to perform the task were provided. If this did not lead to improvements in task performance, the run was stopped and marked as invalid. No feedback was given during the runs. The binaural masking level difference (BMLD) was calculated from the threshold difference between N_0S_0 and the better of the two N_0S_π runs.

2.4.3 Lateralization

For the lateralization task, again a one-octave wide white noise, centered around 500 Hz with an interaural difference in either level or time was presented. The stimuli were generated by copying the same noise sample to both channels and then applying the interaural difference in time or level. The task was to indicate where the sound was perceived inside the head. Responses were given by pressing one of the horizontally aligned numbers '1' to '9' on a computer keyboard, above the letter keys. The participants were instructed to press '1' when the sound was heard on the very left side of their head, '5' for sounds perceived in the center of the head and '9' for the very right side. For possible intracranial positions between the center and the two extremes, the participants were asked to press the respective number '2,' '3,' '4,' '6,' '7,' or '8' on the keyboard. For visual guidance, a template with a schematic drawing of a head indicated the positions of the ears and the center relative to the response buttons. The template covered all of the keyboard except for the numbers '1' to '9.' The duration of the stimuli was 1 s, gated with cosine ramps of 10 ms duration and presented at 70 dB SPL. ITDs ranging from −600 to 600 μs in steps of 200 μs, and two ITDs outside the physiological range (−1500 and 1500 μs), were presented. The ILDs ranged from −12 to 12 dB in steps of 4 dB. The level of the left- and right-ear signals was changed without changing the overall energy by applying the formula presented in Dietz et al. (2013). In addition, monaural stimulation of the left ear and right ear was tested. Each stimulus was presented six times in random order. The diotic stimulus (zero ITD/ILD) was presented eight times. To ensure one common reference system for both types of interaural differences, ILD and ITD stimuli were presented interleaved. In contrast to the investigations by Furst et al. (2000), no training and no center reference were provided in our study. The response to the first trial of each stimulus was not used in further analyses.

Several variables for quantitative description of the lateralization pattern were calculated:

A linear fit to the three left-favoring and right-favoring stimuli, individually for ILD stimuli (−12, −8, −4 dB and 4, 8, and 12 dB) and ITD stimuli (−600, −400, and −200 μs; 200, 400, and 600 μs) was used to describe the steepness of the participants' lateralization percept (*ILD L slope, ILD R slope, ITD L slope*, and *ITD R slope*). The logarithmic ratio of the left and right slope [*ILD slope ratio, ITD slope ratio, e.g., ILD slope ratio = log(ITD slope L/ILD slope R)]* indicates an asymmetric steepness of the two sides.

Variables that inform about side biases in the responses were calculated: The mean of the responses to all ITD or all ILD stimuli (*ITD mean* and *ILD mean*) and the mean of the fit to left-favoring and right-favoring stimuli (*ITD L fit, ITD R fit, ILD L fit*, and *ILD R fit*) were calculated. Furthermore, the mean of those stimuli that were perceived as being in the center of the head (when key '5' was pressed), was calculated for ILD and for ITD stimuli (*ITD center* and *ILD center*). The so-called *diotic percept* was the mean of the responses given for the zero ILD/ITD stimuli.

Another feature of the lateralization data is its variability. For this, the standard deviation for zero ILD/ITD was calculated (*diotic std.*), as well as the mean of the standard deviations of the responses to each ILD stimulus (excluding the monaural stimulation, *ILD std.*), each ITD stimulus (*ITD std.*) and the mean standard deviation of the left-favoring and right-favoring stimuli independently (*ITD L std., ITD R std., ILD L std.,* and *ILD R std.*). Their logarithmic ratios (*ITD std. ratio* and *ILD std. ratio)* can indicate differences in the variability of left-favoring and right-favoring stimuli.

The maximal range of lateralization was calculated by the difference of the maximally lateralized responses given for ITDs within the physiological range (*ITD range*), and for all ILDs excluding monaural stimulation (*ILD range*). The logarithmic ratio of the ranges obtained with ILD and ITD stimuli (*range ratio*) informs about differences in the ranges perceived using the two types of stimuli.

The perception of the monaural left and right (*mon left* and *mon right*), and the ITDs of ±1500 μs (*neg 1500* and

pos 1500) was only evaluated in terms of the mean response to these stimuli.

For all the variables, values within the interval of 1.5 times the standard deviation around the control group mean were considered to be normal. As we did not want to overemphasize possible asymmetries of the left and right side of individual control subjects, we also added the mirrored control data before calculating the mean and standard deviation. With this, the mean was not biased by individual asymmetries and the standard deviation remained unaffected. We verified that adding the mirrored data did not change the results substantially from those obtained without adding the mirrored responses to the data set. Whenever values of the calculated variables are reported, they are in the unit of response keys (a difference of one response button corresponds to 1/8 of the distance between the two ears), except for the variables describing the goodness of fit and the ratios.

3. Results

Analyses will be presented grouped by the presence of stroke (control vs. stroke group) and grouped by the anatomical location of the lesion (lesion groups). In addition, a selected set of individual stroke patients will be shown throughout the results section. These patients are chosen to highlight the individual character of each stroke patient's performance. The color-coding of the eight selected patients is consistent across Figures, allowing for comparison of their measurement results across experiments. In the last subsection, deviations from the control group are shown for individual cases and for lesion groups.

3.1 General assessment

Mean values and standard deviations of the non-auditory testing of the stroke and the control group are shown in Table 1. According to statistical tests (two-sample *t*-tests), the two groups did not differ in age, not in their pure-tone average over the three tested frequencies, and also not in the absolute asymmetry of their left and right PTA3. The scores for the multiple-choice vocabulary intelligence test (MWT-B) and the short form of Beck Depression Inventory (BDI) also did not differ significantly between the groups. In the cognitive screening test (MoCA) however, significantly lower scores were obtained for the stroke group compared to the control group.

3.2 Audiometry

The pure-tone audiometry thresholds for 500, 1000, and 3000 Hz revealed that 35% of the participants had a PTA3 (hearing thresholds averaged over the three frequencies and the two ears) of 20 dB HL or higher, indicating a slight hearing loss (Figure 1). Increased hearing thresholds were especially prevalent at the highest tested frequency of 3000 Hz. Similar PTA3 thresholds were found for the control subjects and for the stroke patients (Table 1), indicating that the pure tone hearing thresholds were not stroke-specific. The selected set of eight stroke patients, indicated by the colored dots, and the two selected control subjects, indicated by the filled gray boxes, span the range of hearing thresholds.

3.3 Correlation analyses

We computed correlations between age and PTA3 and the scores obtained from the general assessment (MoCA, BDI, NIHSS, and MWTB). All correlations were computed for the stroke group and the control group together, because the mean values for the two groups did not differ significantly, except for the MoCA scores (see Table 1). The correlation between age and PTA3 was statistically significant ($\rho = 0.59$, $p < 0.01$). With this, one cannot clearly distinguish between age effects and effects of hearing loss on the other outcome measures. Age and the MoCA score ($\rho = -0.36$, $p < 0.01$) and PTA3 and the MoCA score ($\rho = -0.35$, $p = 0.01$) were negatively correlated. The negative correlation between age and the BDI score ($\rho = -0.28$, $p = 0.03$) was statistically significant, as well. None of the other correlations were statistically significant with the alpha level set to 0.05 (see Table 2 and Supplementary Figure 1).

3.4 Tone-in-noise detection

The majority of participants (44 of the 50 stroke patients, and 11 of the 12 control subjects) produced converging tracks

TABLE 1 General assessment results.

	Stroke $N = 50$	Control $N = 12$	Test statistics
Age [years]	63 (14)	61 (14)	$t(61) = -0.46$, $p = 0.647$
PTA3 [dB HL]	18 (8)	14 (9)	$t(61) = -1.54$, $p = 0.129$
PTA3 asymm. [dB]	4 (4)	5 (4)	$t(61) = 0.65$, $p = 0.518$
MoCA score	23.90 (4.68)	28.36 (1.63)	$t(60) = 3.10$, $p = 0.003$
MWT-B score	29.72 (4.07)	31.37 (4.15)	$t(59) = 1.21$, $p = 0.231$
BDI short score	7.60 (5.04)	6.30 (3.15)	$t(61) = -0.86$, $p = 0.394$

Mean, standard deviation, and *t*-test results for stroke and control groups. Values are given in the form 'mean (standard deviation)'.

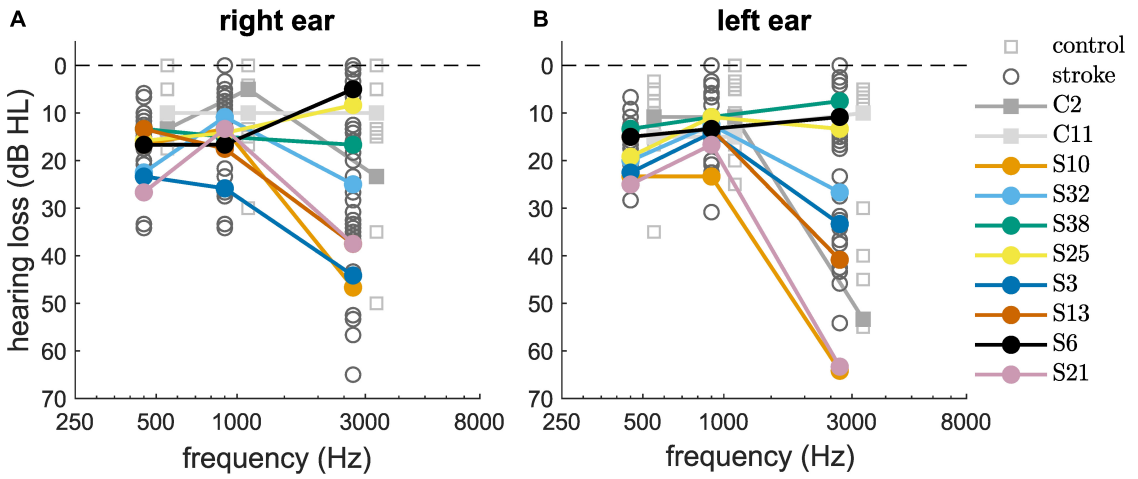

FIGURE 1
Pure-tone audiometric thresholds of the control group (squares) and the stroke group (circles) measured at the right ear **(A)** and left ear **(B)**. Selected participants are highlighted by the color coding used throughout the figures.

TABLE 2 Correlations between age and PTA3 thresholds and the results of the non-auditory measurements (MoCA, BDI, NIHSS, and MWT-B) for stroke and control group together.

	Age [years]	PTA3 [dB HL]
Age [years]	–	$\rho = 0.59$, $p < 0.001$
PTA3 [dB HL]	$\rho = 0.59$, $p < 0.001$	–
MoCA score	$\rho = -0.36$, $p < 0.001$	$\rho = -0.35$, $p = 0.01$
BDI score	$\rho = -0.28$, $p = 0.03$	$\rho = 0$, $p = 0.97$
NIHSS score	$\rho = 0.11$, $p = 0.44$	$\rho = 0.20$, $p = 0.17$
MWT-B score	$\rho = 0.14$, $p = 0.29$	$\rho = -0.18$, $p = 0.17$

in both conditions of the tone-in-noise detection task. The BMLD was calculated from the difference between N_0S_π and N_0S_0 thresholds (see **Supplementary Figure 2**). Four patients (S6, S18, S20, and S24) and one control subject (C3) produced a convergent track only in the N_0S_0-condition, preventing the estimation of the BMLD. S2 and S44 did not produce any converging tracks. It is not known why these participants were not able to perform the task. Due to restricted measurement time, the tasks were not repeated. The normal values of BMLD, as defined by the mean ±1.5 times the standard deviation of the control group results, ranged from 7.5 to 20.1 dB. Of those participants that produced convergent tracks, 93% of the stroke group (41 of 44 patients) showed a BMLD of 7.5 dB or more. This result is comparable to the result from the control group, with 91% of the subjects demonstrating a BMLD of 7.5 dB or more. As shown in **Figure 2** there was a significant negative correlation of the BMLD with age ($\rho = -0.36$, $p = 0.02$), but not with PTA3 ($\rho = -0.22$, $p = 0.11$).

3.5 Lateralization

In general, all participants were able to complete the lateralization task and almost all reported that the monaural stimuli were perceptually different from the binaural stimuli, and that they were the easiest stimuli to lateralize. For many patients, visual inspection of the data did not reveal any impairments in lateralization. Selected group analyses (averages over lesion groups) are presented in **Table 3**. In the following paragraphs, the observed lateralization patterns of the control group and the lesion groups will be discussed in terms of group averages and examples of individual patients.

In particular, data from eight patients with different lesion locations and volumes (see **Figure 3**) were selected for individual presentation. The results of the lateralization task (perceived intracranial position for the presented ILDs and ITDs) are shown in **Figure 4** for two example control subjects (panel A and B) and the eight selected stroke patients (panels C-J). These patients are not fully representative of the average patient for their respective lesion group, but rather display distinct response patterns. The lateralization results of all other participants can be found in the **Supplementary Figures 3–8**.

3.5.1 Control group

Physically left-favoring, to consecutively more right-favoring stimuli, were perceived from the left to the right inside the participants' heads for the ILD and ITD stimuli for all control subjects, with only slight deviations. Apparently, the chosen ILDs, ranging from −12 to 12 dB did not lead to strongly lateralized auditory images (responses close to response keys 1 = left and 9 = right). Previous studies already demonstrated that the extent of perceived lateralization for ILDs

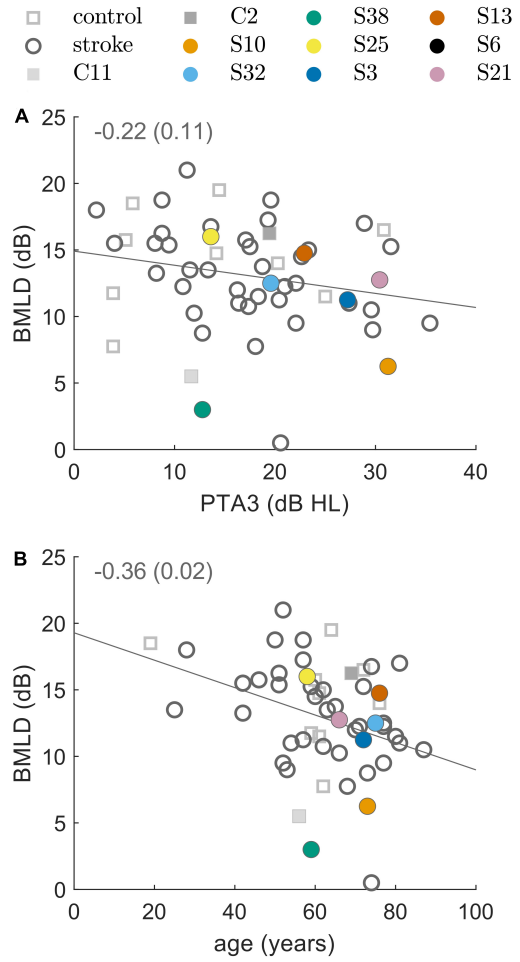

FIGURE 2
Binaural masking level difference (BMLD) resulting from the binaural tone-in-noise detection experiment. BMLD over PTA3 in panel **(A)** and BMLD over age in panel **(B)** for control subjects (squares) and stroke patients (circles). The line represents a linear fit and the inset represents the correlation coefficient and the respective *p*-value. Selected participants are highlighted by the color coding used throughout the figures.

of this magnitude varies across subjects (Baumgärtel and Dietz, 2018). It also depends on frequency, with stronger lateralization perceived for the same ILD magnitude and lower-frequency signals (Bernstein and Trahiotis, 2011). Auditory space was distributed roughly symmetrically around zero ITD/ILD, being reflected in the average perceived position over all ILD and ITD stimuli (*mean*) of 5.2 in the control group. Even in the control group, the perceived intracranial positions were not perfectly distributed around the center (5.0). Monaural left or right stimulation was perceived close to the most lateralized intracranial positions (*mon left*: 1.5 and *mon right*: 8.6) with almost no intra-individual variability. For all ILDs and all absolute ITDs $\leq$ 600 μs, a small variability in single trials can be seen. The standard deviation of given responses was for all stimuli approximately in the range of one response key for the control subjects (e.g., 1.1 for *diotic std.*, the standard deviation of zero ILD/ITD). Only one person of the control group produced much more variable data. The variability of ITDs of ±1500 μs was larger than for smaller ITDs in most control subjects. This unnaturally large ITD was perceived less lateralized compared to smaller absolute ITDs. Based only on the center frequency (500 Hz), one cannot distinguish between a time shift of −500 or +1500 μs, as the period at this frequency is 2000 μs. However, since the stimulus is a white noise of 333 Hz bandwidth centered around 500 Hz, the auditory system can partially resolve this ambiguity, by exploiting either the interaural correlation at other frequencies or the envelope ITD. The *range of lateralization* was larger for ITDs (5.5) compared to ILDs (3.7) and for both interaural differences was much smaller than the maximal possible range of 8.

In the **Figures 4A, B**, examples of data from two typical control subjects (C2 and C11) show the main trends described above. The colored symbols represent the responses to individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. If no asymmetry was present in a participant's responses, they should have the same slope on both sides. Completely symmetrical responses to left-favoring and right-favoring stimuli were obtained only by a small number of control subjects. Obviously, for some individual trials the participants' responses differed from the expected pattern, as for example in one trial with subject C2, the response to monaural-right stimulation was the left-most response key. This intra-individual variability can occur for various reasons. For example, it may be due to perceptual variability *per se*, but could also depend on the state of attention, or lack of concentration when reporting the percept. In **Figures 4C–J**, the general trends observed in the control group are visualized with the gray line and shaded area indicating the mean and the 1.5 times standard deviation interval around the mean response of the control subjects.

Despite the reduced range of lateralization in most participants, different lesion groups were found to be associated with altered lateralization percepts.

3.5.2 Brainstem lesions

In only one of the seven patients with a brainstem lesion (S42) did the lateralization results visually resemble the control group. All the others showed obvious deviations from the control group. In four of the seven patients of the brainstem lesion group (S7, S10, S12, S22, and S32), a reduced set of response keys was used. The responses were given in the categories left–center–right or only left–right. This is partially reflected in the *diotic std.* of 1.8 for this lesion group. Lesions in the brainstem (medulla, pons, or midbrain) did not alter

TABLE 3 Quantification of the lateralization results for the lesion groups.

	Mean	*diotic std.*	*ITD range*	*ILD range*	*mon left*	*mon right*
Control (12)	5.2	1.0	5.5	3.7	1.5	8.6
bs l (3)	5.9	1.2	5.3	5.0	1.5	8.7
bs r (4)	4.8	1.4	4.8	4.0	1.3	8.9
thal l (4)	4.7	1.4	4.3	3.4	2.1	8.3
bg l (7)	4.9	1.3	4.8	3.2	1.9	8.7
bg r (4)	5.6	1.6	4.2	2.8	3.1	7.8
multi l (7)	5.3	1.8	5.5	4.4	1.5	7.9
multi r (9)	5.5	1.3	4.8	3.5	2.3	8.5
occi l (3)	5.1	0.8	4.3	4.0	1.1	8.9
cereb l (2)	5.1	1.4	5.1	3.4	1.3	8.5
cereb r (2)	5.7	1.0	3.8	3.2	1.4	8.7
multi b (5)	5.1	2.3	6	4.4	2.0	8.3

Bs, brainstem; thal, thalamus; bg, basal ganglia; multi, multiple lesion sites; occi, occipital lobe; cereb, cerebellum; l, left; r, right. All values are in the unit of response keys (1 = left, 5 = center, and 9 = right).

the perception of monaural stimuli (average of the left-sided and right-sided lesions for the *monaural left* stimulus: 1.4 and 8.8 for *monaural right* stimulation), except in patient S7. Two examples of this group (S10 and S32) are presented in Figure 4 and discussed below.

Patient S10 (73 years) had a lesion in the caudal medulla to rostral pons on the left side. All stimuli, except for the monaural left stimulus, were perceived in the right hemifield (see Figure 4C). This patient gave no responses between center (key 5) and right (key 9). Especially in the case of ITD, right-favoring stimuli were mainly perceived on the right side, whereas left-favoring stimuli were perceived in the center or at the right ear. For the monaural-left stimulus, however, the patient consistently reported the left-most position. The patient had the maximal possible score in the MoCa, but, with a PTA3 of 31 dB, a mild hearing loss and also a PTA3 asymmetry of 11 dB, with a higher threshold in the left ear. The patient was not using a hearing aid. In the tone-in-noise detection task, the track of the binaural condition (N_0S_π) was initially approximately 10 dB below the monaural condition (N_0S_0). The track finally converged to the monaural threshold, as the interaural information was no longer exploited, leading to a BMLD below the normal range.

A lesion comparable to the case described above, but on the right side, was found in the patient S32 (75 years), and is shown in Figure 4D. The patient never reported a centralized percept (answer keys 4, 5, and 6 were never used) and all stimuli were perceived very close to either ear. The ILD/ITD = 0 stimulus was more often perceived on the left side. Also, both of the supranatural 1.5 ms ITD stimuli were perceived on the left side. This patient had a BMLD of 12.5 dB (within the normal range) and a MoCA score of 22.

Patient S26 (77 years) who was not in the pure-brainstem lesion group, but had multiple lesion sites in both hemispheres, including the left brainstem, also only responded in two categories, but never reported a stimulus to be in the center.

3.5.3 Thalamus lesions

We observed a shift of the auditory space in all patients with a thalamic lesion. However, one left-sided stroke patient showed a shift toward the right side, the other three to the left side. Therefore, the mean responses in this lesion group were only

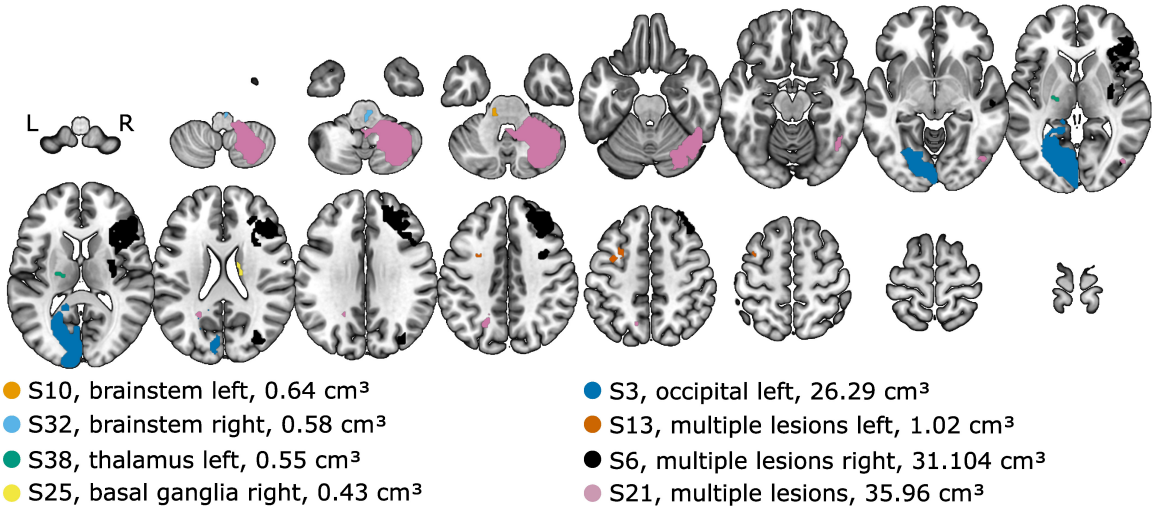

FIGURE 3
Lesion locations overlaid on axial slices of the MNI152 template. The lesion group and the lesion volume is given in the legend. Selected patients are highlighted by the color coding used throughout the figures.

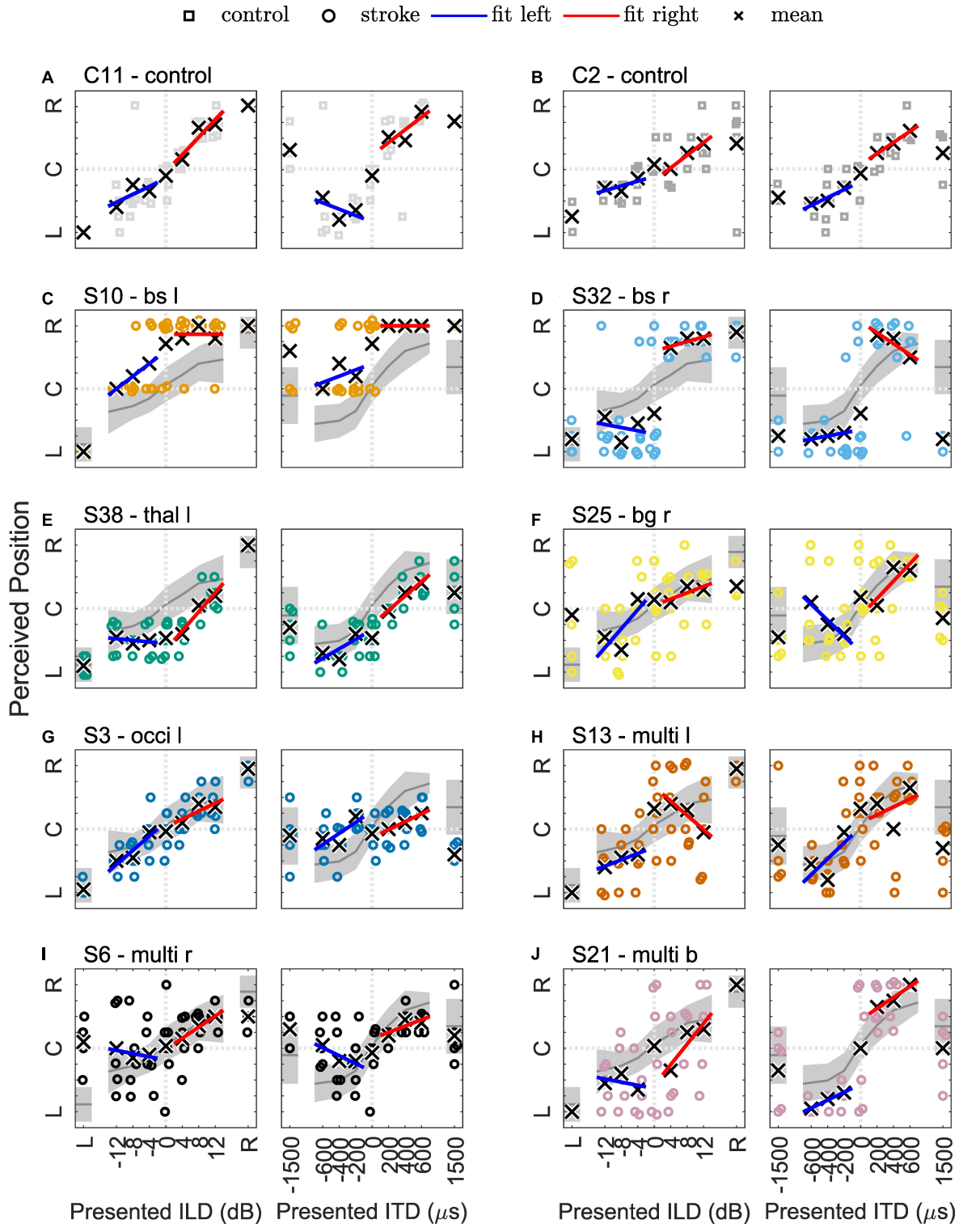

FIGURE 4
Results of the lateralization task for two example control subjects in panels **(A,B)** and eight selected stroke patients in panels **(C–J)**. The colored symbols represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. The gray line and shaded area in panels **(C–J)** indicate the mean and the 1.5 times standard deviation interval around the mean response of the control subjects.

slightly shifted toward the left side (*mean* of 4.7). This also led to a smaller *ITD range* (4.3) and *ILD range* (3.4) than in the control group. In this group, on average, the monaural stimuli were not perceived as much lateralized as in the control group (monaural left: 2.1, monaural right: 8.3). However, this group finding resulted mainly from one patient (S36) that had a high rate of left-right confusions, this was not observed in any other patient of the group.

The patient S38 (59 years) chosen as an example for this group and shown in **Figure 4E** had a very small lesion in the left lateral thalamus (calculated lesion volume = 278 mm^3). This damage seems to have led to a shift in the auditory space toward the left side and a reduced range of lateralization. All left-favoring ILD stimuli and the diotic stimulus were perceived at the same position on the right side, indicating that they were indistinguishable by this patient (see **Figure 4E**). Unlike the other patients with a thalamic stroke, this patient had almost no benefit from binaural listening in the tone-in-noise detection task (BMLD of 3 dB, below the normal range), even though small changes in ITD led to more lateralized percepts. It is unclear, however, if this patient would have improved with more training, as the second run of the N_0S_π condition converged to a lower threshold compared to the first run.

3.5.4 Basal ganglia lesions

Due to the small number of patients in the previously presented groups, comparisons between left-sided and right-sided lesions were not feasible. The basal ganglia lesion group, however, consisted of a larger number of patients (11) with 7 left-sided and 4 right-sided lesions. Comparison of the results between the left- and right-sided lesion cases revealed clear differences in lateralization results. Left-sided basal ganglia lesions resulted in lateralization patterns comparable to the control group. Also, the BMLD for these patients was 10 dB to 19 dB and was thus within the normal range. Patients with right-sided lesions however, showed a higher trial-to-trial variability, compared to the left-sided lesion group. On average, the auditory space of the right-sided stroke group was shifted toward the right side (*mean* of 5.6). Two patients in the right-sided basal ganglia lesion group (S19 and S25) perceived the monaural stimuli more centralized than the control group. One patient (S2) of the right-sided lesion group was not able to carry out the tone-in-noise experiment, while the other three had BMLDs of 11 to 16 dB, within the normal range.

The lateralization results of one of the patients with right-sided basal ganglia damage (patient S25, 58 years) is shown in **Figure 4F**. In this selected patient, the patterns described above (high variability and shift) are also present. The patient had a BMLD within the normal range (16 dB).

3.5.5 Cerebellar lesions

Four patients had lesions in the cerebellum. By visual inspection, in two of them (S4 and S37) the lateralization performance differed from the control group. In patient S4, with a right-sided lesion, almost no change in lateralization for different ITDs could be observed, but a smooth, though flat, transition for ILD-based lateralization. Patient S37 showed no impairments in ITD-based lateralization, but the variability of left-favoring ILD stimuli was larger than for right-favoring ILD stimuli. All BMLDs of this group were within the normal range.

3.5.6 Multiple lesions in one hemisphere

In many cases, stroke lesions were distributed over several cortical and subcortical areas (see, e.g., patient S6 in **Figure 3**). Therefore, this group is especially heterogeneous. Almost all patterns described in the previous groups can be found in some of the patients in this group. In more than half of the cases, large differences to the control group can be observed by visual inspection. The trial-to-trial variability of the given responses was increased in a large number of patients with multiple cortical lesions, even if the auditory cortex was not directly affected (e.g., S23 and S48). Especially contralesional difficulties, as shown by highly variable lateralization responses or a less steep slope in the contralesional hemifield, can be found (e.g., S13 and S20). Interestingly, only in two patients (S6 and S48) was a neglect reported with the NIHSS tests. Both had increased variability on the left (contralesional) side and reported some of the left-favoring stimuli on the right side. For some patients (e.g., S6, S20, and S41) with right-sided cortical and subcortical lesions, the left-favoring and the right-favoring stimuli with an ITD of ± 1500 μs were both perceived on the right (the ipsilesional) side. With multiple lesion sites in the left hemisphere, only one patient (S13) had this ipsilesional shift, whereas two others (S29 and S45) also had a shift toward the right—in this case contralesional side.

Two of three patients with damage to the occipital lobe showed almost normal patterns of lateralization, and BMLDs of 11 dB and 18 dB (within the normal range). The third member of this lesion group (patient S3, 72 years, lateralization results shown in **Figure 4G**) showed almost no sensitivity to ITD-based stimuli, whereas ILDs led to lateralization within the normal range, very similar to the cerebellar stroke patient S4 described above. Compared to the other group members, patient S3 had a slightly reduced BMLD of 8 dB, just within the normal range.

In patient S13 (76 years, presented in **Figure 4H**) damage mainly to the superior frontal lobe on the left side led to an almost normal lateralization performance in the ipsilesional hemifield, but increased variability for the zero ILD/ITD stimulus and right-favoring stimuli. The monaural left and right stimuli and the BMLD were unremarkable and within the normal range.

Patient S6 (62 years) had widespread lesions in the right hemisphere, including temporal and frontal cortex areas, the insula and basal ganglia. This patient showed high variability for the left monaural stimulus, whereas responses to the right monaural stimulus did not vary much from trial to trial (**Figure 4I**). In this patient, the difference between the left and the right hemifield was even stronger than in S13. The responses to right-favoring interaural differences varied very little, whereas the left-sided (contralesional) stimuli varied a lot and were even sometimes reported on the other side. This person also showed signs of neglect that were captured with the NIHSS. Again, the BMLD was not affected.

3.5.7 Multiple lesions in both hemispheres

Compared to the other lesion groups, data interpretation for the patients with multiple lesions distributed in both hemispheres was very difficult. None of these patients showed results similar to the control group.

Patient S21 (66 years), presented in **Figure 4J**, had small lesions in the left precuneus cortex and the right occipital cortex, but a large lesion in the right cerebellum, probably also including small portions of the left medulla. This patient had a NIHSS score of 20 points, but the item on neglect was rated with zero points. Patient S21 showed considerable differences in lateralizing ILD- or ITD-based stimuli. ITD-based lateralization appeared mostly unaffected, whereas the ILD-based lateralization results were shifted toward the left with high trial-to-trial variability. However, this could also be related to the PTA3 difference of 9 dB between the two ears (right ear more sensitive). Nevertheless, responses to stimuli without any interaural difference varied strongly, but adding an ITD of 200 μs or −200 μs already led to strong and reliable right-lateralized or left-lateralized percepts. The BMLD of 13 dB was within the normal range.

3.5.8 Lesions on the primary auditory pathway

This lesion group contains patients for which the MNI-registered lesion outline overlaps to some extent with areas of the primary auditory pathway (subcortically or cortically). These patients are already included in the previous lesion groups. Many patients of this group show distinct lateralization patterns. Three of the selected subjects shown in **Figure 4** had lesions of the auditory pathway. S10 (**Figure 4C**) had a lesion of the left superior olivary complex (SOC), S32 (**Figure 4D**) a lesion of the right SOC, and S6 (**Figure 4I**) a lesion of the right auditory cortex. Altered lateralization patterns were also found for S7 (lesion close to the left cochlear nucleus and SOC) and S31 (lesion between SOC and inferior colliculus). This indicates that direct involvement of the auditory pathway does affect the lateralization in almost all cases. However, in S14 (multiple lesions close to the left SOC and dorsal of the right AC) and S16 (partial overlap with left AC) parts of the auditory pathway seem to be affected without leading to obvious influences on these patients' lateralization performance.

3.6 Differences to the control group

Verbal description of the performance in the two experiments as given above fails to reveal some of the general patterns within specific lesion groups. An attempt to quantify the results of both experiments relative to the control group is shown in **Figure 5**, showing divergences from the control group for all individual patients for different variables calculated from the results of the tone-in-noise detection experiment and the lateralization experiment. For each variable, the upward and downward triangles indicate higher or lower values compared to the normal range (mean ± 1.5 standard deviation) of the control group. The patients are grouped according to the lesion locations. The variables are clustered in group *A* to group *G*, describing different response characteristics. The gray shadings indicate the percentage of deviations from the control results within each specific subgroup (lesion group and variable cluster). For the lesion group 'brainstem left' for example, the percentage of divergences in cluster *A* is approximately 11 percent (one out of nine).

The variables in cluster *A* are the thresholds of the tone-in-noise experiment. For these variables, the strongest divergences were found in the 'thalamus left' lesion group. Cluster *B* consists of variables describing a shift of auditory space. Again, the 'thalamus left' lesion group showed the most divergences for these variables, followed by the groups 'brainstem left,' 'multiple lesions left,' and 'basal ganglia right.' The highest percentage of divergences in cluster *C* (variability of the data) can be observed for the 'basal ganglia right' group, followed by the groups 'brainstem left,' 'multiple lesions bilateral,' and 'multiple lesions left.' The highest percentage of divergences from the control group in variables of cluster *D* are found in the 'brainstem left' lesion group. Cluster *D* is a collection of variables that describe the slopes of the fits. Cluster *E* describes the ranges of ITD- and ILD-based stimuli, as well as the difference between the ranges. Again, the most divergences are found for the group 'brainstem left.' The perception of monaural stimuli (cluster *F*) differed from the control group most for the lesion group 'basal ganglia right,' whereas the large ITDs outside the physiological range (cluster *G*) were perceived differently to the control group by the groups 'brainstem left' and 'brainstem right.'

From the data presented in **Figure 5**, it becomes apparent that lesions in the left basal ganglia, the occipital lobe and the cerebellum did not lead to lateralization patterns that differ from the control group to any great extent (no more than 33 percent), whereas divergences in many variable clusters are found for patients with damage in the brainstem, the thalamus, and right basal ganglia, and for those individuals with multiple lesions in one or both hemispheres. Much stronger differences,

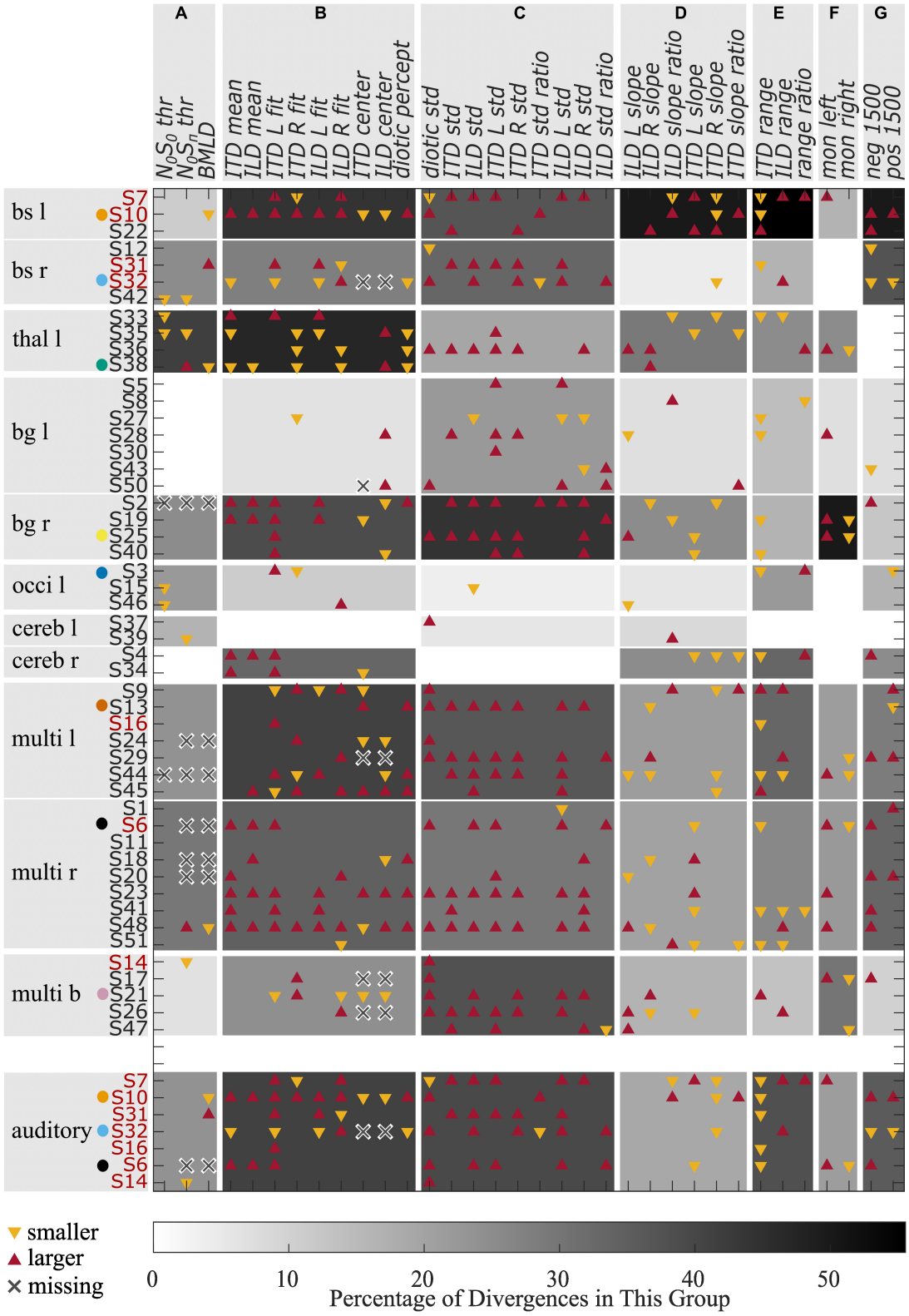

FIGURE 5
Divergences from the control group for different variables. Red upward triangles indicate values of individuals that are larger and yellow downward triangles values that are smaller than the normal values (mean ± 1.5 times standard deviation) calculated from the control group. Crosses indicate missing values. The gray shading indicates the percentage of deviations found within one lesion group for one of the variable groups **(A–G)**. The red font is used for those patients who had a lesion on the primary auditory pathway. Selected patients are highlighted by the color coding used throughout the figures.

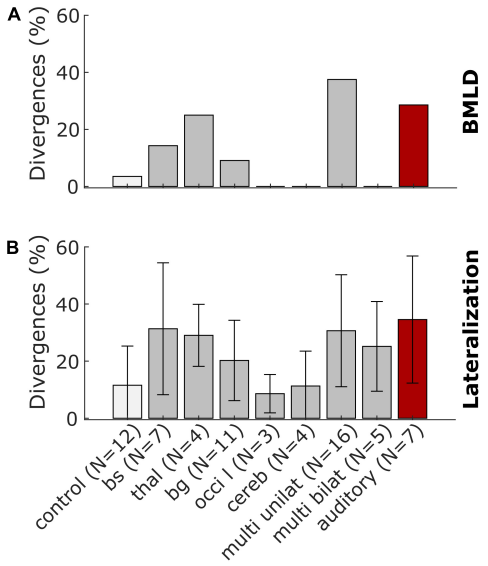

FIGURE 6
Summary representations of the stroke-related binaural hearing deficits across patient groups. Panel **(A)** shows the percentage of patients who had BMLD-values that were worse *(smaller)* than the control group mean by more than 1.5 standard deviations or could not complete the task. Panel **(B)** shows the percentage of possible divergences of all values calculated for the lateralization patterns with error bars denoting the standard deviation across participants for the control and lesion groups.

especially in clusters *B, C,* and *F* are present in those patients with lesions to the right basal ganglia compared to left basal ganglia. Furthermore, all but one of the seven patients who were not able to complete the tone-in-noise detection experiment had multiple lesion sites.

The data presented in Figure 5 was condensed to a simpler representation by extracting the percentage of divergences of the BMLD and a general measure of lateralization performance by averaging over the number of divergences of all variables in clusters *B*-*G*. Lesion groups were pooled over left-sided and right-sided groups. The value for these simplified BMLD and lateralization measures are shown in Figures 6A, B, respectively. Note, that panel A represents the percentage of patients showing smaller than normal or non-convergent tracks in the BMLD task, whereas panel B represents the mean percentage of possible deviations in a given group with the error bars denoting the standard deviation across participants in the group.

For two of eleven patients with lesions in the brainstem or the thalamus, the BMLD diverged from the normal values. One patient of each lesion group had a BMLD of less than 7.5 dB. One patient with a lesion of the basal ganglia and five of 16 patients with unilateral cortical lesions did not produce converging tracks in the task, representing the most remarkable divergence in this task. No divergences were observed for the other lesion groups (see Figure 6A). Two of seven patients with a lesion on the primary auditory pathway diverged from the normal values. One of these two patients produced a BMLD of 6.25 dB, the other one did not produce converging tracks in the dichotic condition of the task. In general, deviations of the BMLD were not frequently observed in the stroke group.

In contrast, for all lesion groups, divergences in terms of the lateralization pattern are found (see Figure 6B). Both measures have the highest percentage of divergences for the patients with a lesion on the primary auditory pathway as shown with the red bars in Figure 6.

4. Discussion

In the present exploratory study, our aim was to investigate the binaural perception of individuals in the acute phase of stroke. The performance of the stroke patients in two binaural headphone experiments and the results of the general assessment were compared to an age-matched control group. To our knowledge, this was the first time that the same binaural hearing tasks were conducted in acute-phase stroke patients with various lesions, ranging from the brainstem up to cortical areas. Interpreting these data is a challenging endeavor, especially for the results of the lateralization task, where several metrics are possible and necessary. Using various approaches of comparing patients on a group level and individually with the control group, we found impaired binaural hearing in the majority of stroke patients as shown in Figures 5, 6.

One of the most prominent results was that some of the brainstem-lesion patients lateralized ITD and ILD stimuli in a categorical manner, as suggested by the fact that only a reduced set of response keys was used. For instance, some of these patients commonly gave responses in the categories left-center-right or only left-right, with no responses at intermediate positions. As the information from the left and right ear is integrated in brainstem nuclei for the first time, strongly altered lateralization patterns were expected for the patients who had suffered a stroke to these structures. Accordingly, some of the most prominent distortions in spatial perception were found for brainstem lesion patients. For instance, the cases without responses in the center position were almost exclusively associated with damage of the brainstem (e.g., S32). For this lateralization pattern, at least two interpretations are possible. First, it is possible that a fused image was perceived, but it was lateralized very much toward the sides. An alternative explanation would be that binaural fusion failed for these subjects. As a result, they might have perceived split auditory images (two separate sound sources rather than a single fused image) and reported the position of the dominant image. This ambiguity could be resolved by asking for the number of perceived sound sources in any subsequent studies. The described pattern of side-oriented lateralization was also reported by Furst et al. (2000) for lesions in rostral parts of

the brainstem. In contrast to their findings, we did not observe center-oriented patterns (consistently no lateralized percept) in any of the patients from the brainstem lesion group. Despite the many differences between the brainstem patients and the control group as seen in **Figure 5**, both ILD and ITD stimuli evoked lateralized percepts in all but one patient (S31) of this lesion group. The mean responses of this patient were close to center for all ILD stimuli and left-sided ITD stimuli. The patient had a reduced ITD range, but also a larger standard deviation than the control group. This pattern of responses is suggestive of reduced sensitivity to interaural cues rather than of a center bias.

Left-sided thalamic lesions were, in all cases, correlated with a shift in the lateralization results for both ILD and ITD stimuli. This becomes clear from the high prevalence of deviations in cluster *B* of this group shown in **Figure 5**. Three out of four patients of this lesion group showed a shift toward the ipsilesional side. No conclusion on the effects of left- vs. right-sided lesions can be drawn, because none of the patients in this study had a lesion of the right thalamus. In addition, one subject with a thalamic lesion displayed remarkably high trial-to-trial variability in their lateralization responses. The medial geniculate nucleus (MGN) located in the auditory thalamus receives projections from the ipsilateral and contralateral inferior colliculus and projects to the ipsilateral auditory cortex (Pickles, 2013). Assuming that these projections are damaged by the stroke, one possible explanation for the lateralization shifts could be that corrupted inputs reach the MGN. Higher variability could be related to altered inputs to the cortical representation stages (outputs of the MGN). Besides damage to auditory nuclei, shifts in auditory space could also be related to asymmetrical hearing thresholds (Florentine, 1976). The hearing thresholds at 500 Hz were symmetrical between the two ears in all patients of this lesion group (except for the one with the increased trial-to-trial variability), but the PTA3 asymmetry was in a range of 4 to 13 dB and pointed toward the direction of the shift. This is in agreement with a significant correlation of PTA3 asymmetry with both ILD mean ($\rho = 0.34$, $p = 0.017$) and ITD mean ($\rho = 0.34$, $p = 0.016$) when including all patients of the stroke group. Even though the PTA3 asymmetry can influence the results of the lateralization task, the finding of shifted auditory space for all thalamic-lesion patients indicates an influence of the left thalamus on lateralization. This is in line with previous studies that have found a connection between thalamus lesions and visuospatial neglect (Karnath et al., 2002).

A biased auditory egocentric space in cases with inferior parietal and frontal dysfunction was reported by Bellmann et al. (2001). Further, they found an imbalance of attentional load allocated to the left and right hemispaces (hemispatial inattention) following lesions of basal ganglia and insular cortex. Both mechanisms (biased spatial perception and unbalanced spatial attention across hemifields) come into play for our lateralization task, but their effects are difficult to distinguish in our data. Shifted auditory space and altered lateralization slopes (steepness of the lateralization function of ITD/ILD, see, e.g., S38) indicate distortions of spatial representation. Increased trial-to-trial variability, on the other hand (e.g., S13 and S25), may be indicative of attentional or cognitive impairments, or both. Also, Gutschalk and Dykstra (2015) concluded that more work is needed to develop clinical protocols that can clearly distinguish localization deficits from disorders of spatial cognition. The effects of the right basal ganglia on the lateralization patterns that we observed, could be attributed to attentional deficits. In contrast to Bellmann et al. (2001), our results show that the perception of both left-favoring, as well as right-favoring stimuli was affected in some patients (see **Figure 5**). Given the supra-modal nature of the neglect syndrome, a basal ganglia lesion may affect auditory and visual hemispatial attention. Influences of right basal ganglia lesions on the visuospatial perception of both, ipsi- and more frequently contralesional stimuli were already reported by Karnath et al. (2002).

For almost all patients with multiple lesions in one or both hemispheres, we found lateralization patterns that differed from the control group in terms of increased variability and decreased slopes, as shown by the high number of divergences in the clusters *C* and *D* of **Figure 5**. Besides contralesional deficits as in patient S6 with multiple lesion sites, including the right temporal lobe, many patients also displayed ipsilesional deficits for both left- and right-sided lesions. This is only partially in line with previous literature (see Häusler and Levine, 2000 for a review) that suggests a dominance of the right hemisphere in auditory spatial representation. In our study, a comparison of left-sided and right-sided cortical lesions might not be meaningful, because of the unequal distribution of lesion sites. Since the inability to understand and produce speech is mainly observed after damage to left-hemispheric language areas, and was one of the exclusion criteria, left-sided and right-sided groups differed in terms of their lesion locations. For basal ganglia lesions however, strong differences between the left and right side were observed, with more frequent and more severe deficits after right-sided lesions than for left-sided lesions. This result is similar to the results presented in Karnath et al. (2002) for the visual modality.

The perception of ± 1500 μs ITDs, i.e., ones that are larger than those usually experienced under natural listening conditions, was only rarely affected. In the brainstem-lesion patients S10, S22, and S32, the left-favoring and right-favoring stimuli were both perceived on the contralesional side. The ambiguity of this stimulus stems from the conflicting interaural cues conveyed by the envelope (indicating the position on the leading side) and the temporal fine structure (indicating a stimulus on the opposite site). With damage in one side of the brainstem, the ipsilesional cue may not be accessible to the next processing stage or less weight might be given to it. With multiple cortical and subcortical lesions, the outcomes are more diverse. While some patients (e.g., S13 and S20) perceived

both of these stimuli only on the ipsilesional side, other patients (e.g., S29 and S45) perceived them exclusively on the contralesional side. These findings point to the interpretation that disturbances at different levels of ITD representation stages can lead to stimuli with unnaturally large ITDs being perceived at different intracranial positions. Coding of such large ITDs was already found to differ at midbrain, compared to cortical, levels (Thompson et al., 2006; Kriegstein et al., 2008). While the exact combination of computational processes by which the auditory system encodes ITDs remains elusive, stroke lesion studies such as the present one could potentially aid in their elucidation. However, due to the rarity of psychoacoustic data from stroke survivors, combined with the highly individual nature of stroke lesions, more data is needed before meaningful interpretations are possible.

The dichotic tone-in-noise detection task is a better test for the implicit use of interaural differences compared to the more commonly used measurements of just-noticeable differences in ILD and ITD cues. In many cases, the performance in these tasks depends on the explicit perception of intracranial positions rather than on the general ability to exploit binaural cues for unmasking. To be able to directly compare the results of the implicit tone-in-noise detection task with those of the explicit lateralization task, we refrained from using speech-related tasks such as the one used in, e.g., Tissieres et al. (2019). The results of our lateralization task revealed that five of the six patients with lesions in the right basal ganglia showed remarkable impairments in ITD-based lateralization, which requires the explicit use of interaural differences. Four of these five patients had a BMLD in the normal range (and one only slightly below the normal range), indicating that they had access to implicit ITD information, despite the fact that they could not exploit ITDs explicitly in the lateralization task. This reveals that altered ITD-based lateralization is not necessarily related to dysfunctional encoding at the primary stage in the superior olivary complex. Instead, it seems that damage to the explicit representation stages can impair lateralization even if the primary encoding stages remain unaffected. In general, few patients had smaller than normal BMLDs. Similarly, also Lynn et al. (1981) reported that the speech BMLD was not affected in patients with lesions on cerebral, thalamic, midbrain or rostral pontine levels. In their study, only patients with lesions at the ponto-medullary level showed a reduced BMLD. In our study, two patients had a lesion at the ponto-medullary junction. One of these two patients had a reduced BMLD. Only two of the remaining 48 patients with lesions at other areas had a reduced BMLD. Due to these low numbers, no clear supporting or contradicting conclusions can be drawn. On the other hand, the inability to do the tone-in-noise detection task (missing values due to non-convergent tracks, indicated by crosses in **Figure 5**) was observed in some patients in which, among other areas, the basal ganglia were damaged and in some patients also frontal cortical areas. Cortico-striatal loops have been shown to be involved in auditory discrimination learning (Znamenskiy and Zador, 2013), which is a necessary ability for this experiment. This implies that the slightly more complex tone-in-noise detection task needs to be learned first, and may therefore not be an optimal measure of the accessibility of implicit interaural information for participants with learning difficulties. Besides the theoretical implications, the deviations in the BMLD as shown in **Figure 6**, and in particular the inability to complete the task, could be of clinical interest. The BMLD is correlated with age, but the occurrence of stroke does appear to constitute an additional factor affecting binaural tone-in-noise detection performance for some stroke patients. As such, the BMLD could potentially be used clinically to detect effects of stroke on binaural hearing.

Due to the heterogeneous group of participants and the highly individual nature of stroke lesions, the present study is affected by a number of confounding factors. We sought to capture some of these by additional auditory and non-auditory measures such as the audiometry and the MoCA. To paraphrase Gallun (2021), the perturbations caused by nature and not manipulated in the laboratory are never uniform and not easily documented.

In the present study, the selection of patients could not control for the influence of age and hearing loss, but the control group was age-matched and did not differ significantly in their hearing thresholds or in the results of the general assessment. Only the results of the MoCA differed significantly between the stroke and control groups (see **Table 1**). Almost all non-stroke-related difficulties should be rather equally present in both groups. We therefore concluded that the observed effects on a group level, though not on an individual level, can be attributed to the stroke and possible comorbidities, rather than on hearing loss. The selection of those cases presented in **Figures 3**, **4** was based on the results of the lateralization task. The selected stroke patients span the whole range for all measured variables (see **Supplementary Figure 1**). For the stroke patients, of course, the premorbid performance is not known.

The stimuli of both experiments were chosen to be centered around 500 Hz, which is usually spared by age-related hearing loss. The threshold for this frequency was on average 16 dB HL and did not exceed 35 dB HL for any participant. No more than a 10 dB difference between the left and right side was measured at this frequency for any of the participants. We therefore did not expect large influences of hearing loss or asymmetrical hearing abilities on our results. Nevertheless, as discussed above, a correlation of PTA3 asymmetry and shifted auditory space was found.

We focused only on those lesions that had a high signal on the DWI and a low signal in the ADC map, thus representing restricted diffusion. In many cases, older lesions and other damage to brain tissue were present that could have influenced performance in the different tasks. However, improvements from diaschisis or functional reorganization is

known to drive neurologic recovery already in the acute phase (Sang-Bae and Byung-Woo, 2013). In addition, in healthy subjects, reorganization of lateralization with altered ITD cues occurs within few days (Trapeau and Schönwiesner, 2015). This suggests, that binaural hearing impairments are dominated by the acute damage and less by old lesions. Complete lesions of specific parts of the brain are used to study the system in ablation studies in animals. In our patients however, the damage does not necessarily include entire brain structures and may leave some functioning neuronal processing. Furthermore, as pointed out by Neff et al. (1975), experiments in well controlled ablation studies in animals measure the functioning of the remaining system and not necessarily the functioning of the damaged part. In contrast to such ablation studies, the general state of brain structures that were not damaged by the acute stroke varied widely in our population. The observed variability in performance must therefore be partially attributed to differences in the damages as well as to differences in the remaining brain structures, rather than solely to the acute stroke lesion.

Not only did individual characteristics of the patients affect the data, but also external constraints such as the restricted time for the behavioral experiments. The short time we had with the patients did not allow for dedicated training runs nor for repetitions of any task. One example where more time would have been necessary was when patients were not able to do the tone-in-noise experiment. In retrospect, from the trend in these patients' adaptive tracks, it appeared as if some of these patients would have learned to do the task had there been more runs of the same experiment. In addition, the hospital room in which the study was conducted was comparably quiet, but had no sound booth. Finally, the fact that some lesion groups contained only two patients, allowed only limited interpretations. Differentiation between the effects of lesions of a particular anatomical structure as opposed to differences between left-sided and right-sided lesions of that brain area is restricted.

From the data obtained in our experiments, we do not know if these patients also had difficulties in free-field-localization tasks, in which spectral cues are available in addition to natural combinations of ILDs and ITDs. However, as both cues are often perceived with a similar bias and spectral cues are less salient in elderly listeners, we assume that some patients will have localization biases, at least during the acute phase. If a bias remains in the chronic phase of stroke, individualized ILD- and ITD-manipulating algorithms could potentially be exploited to improve localization performance (e.g., Brown, 2018).

5. Conclusion

This exploratory study revealed some expected divergences in binaural perception between the results of patients with acute ischemic stroke lesions and the results of the control group: Impaired contralesional lateralization was found after right cortical and brainstem lesions, which is consistent with previous reports. Other findings could be expected, based on today's understanding of binaural processing and decoding of spatial cues: The perception of binaural stimuli with unnaturally large ITDs is affected differently based on the lesion location. Other findings were less expected, such as the shift in auditory space in all patients with thalamic lesions or the large difference induced by left and right basal ganglia lesions. In contrast to previous reports, no apparent hemispheric difference from cortical lesions regarding the variability of lateralization data were found, and the binaural benefit in the tone-in-noise detection task was unaffected in most patients, although many patients with multiple lesion sites could not complete this task. While it may be too early to suggest any revisions to our understanding of interaural cue encoding or decoding, the outcomes may nevertheless foster more focused future investigations in selected groups of patients with specific lesions, or in animal models. Investigating acute-phase stroke patients may even be an additional avenue to deepen our understanding of the healthy auditory system in a way that is difficult when studying the healthy system in isolation.

Data availability statement

The dataset analyzed for this study can be found at https://doi.org/10.5281/zenodo.7415436. Due to ethical restrictions, only the lesion masks, but no raw MRI images, are provided. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Research Ethics Board of the University of Oldenburg, Germany. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AD, MD, and PS contributed to the conception and design of the study. AD, MD, PS, and KW planned the experimental procedures. AD organized the data base, performed the analysis, and wrote the first draft of the manuscript. MB and AM recruited participants and acquired data. AD, PS, and BS did MRI analyses. AD and MD interpreted the data. MD and HP wrote further sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1022354/full#supplementary-material

A figure with the correlations between age and PTA and the general assessment scores and the tone-in-noise-detection thresholds, and the lateralization results, such as those presented in **Figure 4** for all control subjects and all stroke patients, are available as supplementary data.

SUPPLEMENTARY FIGURE 1
Scatter plots representing correlations between age and PTA3 thresholds and the results of the non-auditory measurements (MoCA, NIHSS, BDI, and MWT-B) for the control group (squares) and the stroke group (circles). In each subpanel, linear-regression lines, the Pearson correlation coefficient ρ, and the respective *p*-value are shown in the form "ρ (*p*-value)". Selected participants are highlighted by the color coding used throughout the figures.

SUPPLEMENTARY FIGURE 2
Results of the binaural tone-in-noise detection experiment. Tone-in-noise detection thresholds for $N0S_{\pi}$ condition (up- and downward triangles for stroke and control subjects, respectively) and N0S0 condition (left- and right-pointing triangles) over PTA3 **(panel A)** and over age **(panel B)**. In each subpanel, linear-regression lines, the Pearson correlation coefficient ρ, and the respective *p*-value are shown in the form "ρ (*p*-value)". Selected participants are highlighted by the color coding used throughout the figures.

SUPPLEMENTARY FIGURE 3
Results of the lateralization task for patients S1–S10. The circles represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. The gray line and shaded area indicate the mean and the 1.5 times standard deviation interval around the mean response of the control subjects.

SUPPLEMENTARY FIGURE 4
Results of the lateralization task for patients S11–S20. The circles represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. The gray line and shaded area indicate the mean and the 1.5 times standard deviation interval around the mean response of the control subjects.

SUPPLEMENTARY FIGURE 5
Results of the lateralization task for patients S21–S30. The circles represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. The gray line and shaded area indicate the mean and the 1.5 times standard deviation interval around the mean response of the control subjects.

SUPPLEMENTARY FIGURE 6
Results of the lateralization task for patients S31–S40. The circles represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. The gray line and shaded area indicate the mean and the 1.5 times standard deviation interval around the mean response of the control subjects.

SUPPLEMENTARY FIGURE 7
Results of the lateralization task for patients S41–S50. The circles represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. The gray line and shaded area indicate the mean and the 1.5 times standard deviation interval around the mean response of the control subjects.

SUPPLEMENTARY FIGURE 8
Results of the lateralization task for control subjects C1–C12. The squares represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively.

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3 | Project II: Does binaural perception change across the different phases of stroke recovery?

In this chapter the research article "Longitudinal Observations of the Effects of Ischemic Stroke on Binaural Perception" is presented. The article was published in 2024 in Frontiers in Neuroscience (https://doi.org/10.3389/fnins.2024.1322762).

This study aimed to get insight into the recovery of impairments in binaural perception caused by stroke. A subgroup of the patients that took part in the acute phase measurements (Dietze et al., 2022, Front. Neurosci. 16:1022354, presented in Chapter 2) repeated the experiments in the subacute and chronic phases of stroke. The results of the lateralization task, the tone-in-noise detection task, cognitive assessments, depression screening, and audiometric testing were compared across the three phases of stroke recovery. At the group level, the performance on the two binaural tasks remained quantitatively consistent. The good results obtained in the tone-in-noise detection experiment in the acute phase remained mostly unchanged in the later phases. However, some patients' lateralization performance improved, whereas for others it deteriorated over time. These trends were not consistent for patients with similar lesion locations, suggesting a highly individual recovery process.

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Contributions:
AD, MD, and PS contributed to the conception and design of the study. AD, MD, PS, and KW planned the experimental procedures. AD collected the data, organized the database, and performed the analysis. AD and MD interpreted the data. AD wrote the first draft of the manuscript. MD and HP wrote further sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Longitudinal observations of the effects of ischemic stroke on binaural perception

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Acute ischemic stroke, characterized by a localized reduction in blood flow to specific areas of the brain, has been shown to affect binaural auditory perception. In a previous study conducted during the acute phase of ischemic stroke, two tasks of binaural hearing were performed: binaural tone-in-noise detection, and lateralization of stimuli with interaural time- or level differences. Various lesion-specific, as well as individual, differences in binaural performance between patients in the acute phase of stroke and a control group were demonstrated. For the current study, we re-invited the same group of patients, whereupon a subgroup repeated the experiments during the subacute and chronic phases of stroke. Similar to the initial study, this subgroup consisted of patients with lesions in different locations, including cortical and subcortical areas. At the group level, the results from the tone-in-noise detection experiment remained consistent across the three measurement phases, as did the number of deviations from normal performance in the lateralization task. However, the performance in the lateralization task exhibited variations over time among individual patients. Some patients demonstrated improvements in their lateralization abilities, indicating recovery, whereas others' lateralization performance deteriorated during the later stages of stroke. Notably, our analyses did not reveal consistent patterns for patients with similar lesion locations. These findings suggest that recovery processes are more individual than the acute effects of stroke on binaural perception. Individual impairments in binaural hearing abilities after the acute phase of ischemic stroke have been demonstrated and should therefore also be targeted in rehabilitation programs.

KEYWORDS

binaural hearing, psychoacoustics, brain lesions, lateralization, binaural masking level difference, magnetic resonance imaging, stroke

1 Introduction

In ischemic stroke, the blood flow through the brain is suddenly disrupted by an acute blockage of blood vessels. The brain regions that are supplied with oxygen and nutrients by these blocked blood vessels can be damaged, which can result in various symptoms, including motor deficits, cognitive decline, and sensory impairments. Consequently, stroke is one of the leading causes of disability in Germany (Robert-Koch Institute, 2017) and globally the second leading cause of death (World Health Organization, 2020). After stroke, recovery of overall

functional ability, including the sensory domain, is typically observed, with the majority of recovery occurring within the first weeks to months (i.e., the acute and subacute phases of stroke), with only reduced recovery thereafter (Skilbeck et al., 1983; Lee et al., 2015). The acute phase of stroke spans the first 7 days, and the subacute phase extends up to 6 months after stroke onset. After that, the patients are in the chronic phase of stroke. In addition to compensatory behaviors, it has been shown in various studies that adaptive and maladaptive neuroplasticity allows the nervous system to respond to intrinsic and extrinsic stimuli by a reorganization of its structure, function, and connections (Cramer et al., 2011).

As described by Chen et al. (2021), the BEFAST scale is a widely used system to identify stroke by detecting problems related to balance, eyes, face, arm, speech, and time (i.e., motor deficits, cognitive decline, and sensory impairments). For example, contralesional impairment, such as difficulties in moving the right arm after a lesion of the left motor cortex, is a well-known symptom of stroke. Also, visuospatial impairment, especially the phenomenon of spatial neglect, is often observed after right-hemispheric ischemic stroke (Heilman and Valenstein, 1979). Unilateral spatial neglect has been associated with impairments of spatial representation or spatial attention (Guilbert et al., 2016).

Simple hearing tasks, such as pure-tone detection, are rarely affected by stroke. According to Häusler and Levine (2000), this is due to two factors: First, many structures early in the auditory pathway, such as the cochlear nucleus, the inferior colliculus, and the medial geniculate body, have multiple sources of blood supply. Second, the bilateral structure and hemispheric crossings at and above the level of the superior olivary complex create redundancy of information in the two brain hemispheres. This leads to the phenomenon that abnormalities in hearing tasks (except for speech understanding and production, which is predominantly represented in the left hemisphere) often only occur in bilateral lesions (Häusler and Levine, 2000).

More complex hearing tasks, such as localizing sound sources in the horizontal plane and benefiting from spatially separated target and distractor sounds, rely on binaural hearing. Interaural differences in time (ITD) and interaural level differences (ILD) are used for binaural hearing. The extraction of ITD and ILD requires an integration of the signals captured at the left and right ear, which occurs for the first time in the brainstem, more precisely in the superior olivary complex, with representations at higher stages (e.g., Goldberg and Brown, 1969). Accordingly, lesions in different areas of the brain, including structures of the primary auditory pathway below and above the superior olivary complex, and several structures in the right and partially also in the left cerebral hemisphere, can disrupt binaural processing, as shown in several preceding studies (Jenkins and Masterton, 1982; Bisiach et al., 1984; Aharonson et al., 1998; Spierer et al., 2009). Rarely, studies of the phenomenon of spatial neglect also included investigations of its effects on the perception of sounds (Gokhale et al., 2013). In general, less is known about stroke-induced effects on binaural hearing abilities compared to other modalities, especially to the visual domain. The aforementioned studies demonstrated difficulties in spatial hearing tasks, each for a specific lesion location. Including patients with different lesion locations in the same study revealed very diverse effects on binaural hearing for lesions at different locations (Dietze et al., 2022).

In the free field, ILD, ITD, and spectral cues lead to spatial perception (localization) of sound sources, because they depend on the incidence angle and the frequency of the sound (e.g., Thompson, 1882). In headphone experiments, it is possible to manipulate ILD and ITD cues independently. A presentation of unnatural ITD - ILD combinations or ILDs without the natural frequency dependence leads to an intracranial perception of sound sources that can be either in the center of the head or perceived closer to one of the ears, which is referred to as lateralization. These unnatural modifications of auditory inputs can be used to investigate ITD- or ILD-specific processing deficits that might not be detectable when both cues are congruent and spectral cues are present, as in free-field sound-localization experiments.

In psychoacoustic experiments with healthy participants, altered binaural cues lead to distorted sound source localization at first, but they partially adapt within a few days of exposure (see Wright and Zhang, 2006 for a review). One example is the 50% reduction of localization bias caused by an artificially introduced ITD bias (Javer and Schwarz, 1995). A larger ITD bias in patients with a hearing aid in one ear and a cochlear implant in the other ear, however, cannot be compensated for by the auditory system and requires a technical latency compensation (Angermeier et al., 2023). Another method is the unilateral wearing of earplugs which leads to localization distortions toward the open ear at first but decreases over the course of 5 days of extensive training (Florentine, 1976; Butler, 1987). Also, experiments conducted under water showed training effects on sound source localization with altered binaural cues (Feinstein, 1973). Due to the higher speed of sound and a reduced head-shadow effect, ITDs and ILDs are diminished under water. Importantly, only specific acoustic features appear to be relearned. Re-learning does not always generalize to non-trained stimuli (reviewed by Keuroghlian and Knudsen, 2007) and adaptations to altered spatial cues are faster with training, compared to exposure (Mendonça, 2014). Following the various findings of at least partial adaptation to altered binaural information in healthy participants, and the reports of functional recovery following stroke (e.g., Skilbeck et al., 1983; Cramer et al., 2011; Lee et al., 2015), partial or full recovery of binaural perception is also expected for clinical populations such as the patients with mild symptoms of stroke, as described in Dietze et al. (2022).

To the best of our knowledge, there has been no study of the longitudinal development of binaural hearing performance after ischemic stroke. Most studies were conducted in the chronic phase of stroke, and only a few in the acute phase, but none included more than one measurement. Exploring the longitudinal effects of ischemic stroke on binaural hearing is important for two reasons: First, to gain a deeper basic knowledge of binaural processing, and second, to understand the mechanisms of recovery, and thus in consequence being able to improve auditory rehabilitation after stroke.

In this study, we aimed to quantify the effects of ischemic stroke on binaural perception in a population of stroke patients with only mild symptoms (according to their clinical stroke score) and with different lesion locations via longitudinal measurements in the acute, subacute, and chronic phase of stroke. Recovery of binaural performance was hypothesized for this group of patients whose lateralization was impaired in the acute phase of stroke, despite almost no clinical signs of stroke.

2 Methods

The experimental methods used in this study are identical to those reported in Dietze et al. (2022). Whenever applicable, only a summary is given here. Where all details are necessary, we quote directly from Dietze et al. (2022).

2.1 Measurement phases

The study consisted of three measurements. The same experiments were conducted on all three appointments. The first measurement was in the acute phase of stroke, on average 5 days after stroke onset (results were presented in Dietze et al., 2022). The second was in the subacute phase of stroke, on average 30 days after stroke onset. The third measurement was in the chronic phase of stroke, on average 306 days after stroke onset.

2.2 Participants

The pool of participants is a subset of the 50 stroke patients measured in the study by Dietze et al. (2022) and 12 control subjects (mean age of 61 years, SD: 14 years, 9 female, 3 male). Participants that had a stroke will be referred to as patients, whereas those participating in the control group will be referred to as control subjects. Patient identifiers (e.g., S32) are the same as in the preceding paper to allow for comparisons between the two papers. Of the 50 patients who participated in the acute phase measurements as reported by Dietze et al. (2022), 19 did not participate in any measurement after the acute phase. Consequently, they were excluded from the analyses of the current study. 31 patients participated in at least one of the later measurements, allowing longitudinal comparisons. These 31 patients included 12 with left-sided lesions (1 brainstem lesion, 3 thalamus lesions, 4 basal ganglia lesions, 2 occipital lobe lesions, 2 multiple lesion sites), 15 with right-sided lesions (3 brainstem lesions, 3 basal ganglia lesions, 1 cerebellar lesion, 8 multiple lesion sites), and 4 with bilateral lesions.

Just as described in Dietze et al. (2022), both groups (stroke patients and control subjects) participated after passing audiometric and cognitive assessments (see sections 2.5.1 and 2.3 for details) and providing written informed consent. The study was approved by the Medical Research Ethics Board of the University of Oldenburg, Germany. The stroke patients were recruited in the stroke unit of the Evangelisches Krankenhaus, Oldenburg, Germany. Only those patients participated, who could understand and produce speech, who were mobile and in a general stable condition, and able to complete the different tasks despite their recent stroke. Exclusion criteria were additional neurological diseases or a pure-tone average of 40 dB HL or more (see section 2.5.1). The control group was age-matched and followed the same exclusion criteria. A subset of 15 patients did the experiments in all three measurement phases (acute, subacute, and chronic).

2.2.1 Acute phase measurements

Analyses for the acute phase measurements are based on the 31 patients who participated in at least one of the later measurements (mean age of 61 years, SD: 15 years, 11 female, 20 male). They were tested in a quiet room at the Evangelisches Krankenhaus, Oldenburg, Germany, on average 5 days (range: 2–8 days) from stroke onset. The National Institute of Health Stroke Scale (NIHSS) was obtained as part of the clinical routine 24 h after the patients came to the hospital. It revealed that the patients only suffered from minor stroke symptoms. The scores of the patients ranged from 0 to 5 points with a median of 1 point (the maximum possible score is 42, with higher scores indicating worse signs and symptoms of ischemic stroke). In none of the patients symptoms of neglect were reported with the NIHSS tests and also the star cancelation task revealed no visual spatial neglect.

2.2.2 Subacute phase measurements

A subset of 24 patients (mean age of 58 years, SD: 15 years, 9 female, 14 male) participated in the experiments in the subacute phase of stroke. They were tested in a quiet room at the Rehazentrum Oldenburg, Germany, on average 30 days (range: 23–39 days, 13 days for S27) after stroke onset.

2.2.3 Chronic phase measurements

A subset of 22 patients (mean age of 65 years, SD: 14 years, 6 female, 16 male) participated in the experiments in the chronic phase of stroke. They were tested in an acoustically shielded chamber at the University of Oldenburg, Oldenburg, Germany, on average 306 days (range: 216–391 days, 500 days for S51) after stroke onset.

2.3 General assessment

Identical to the study in the acute phase (Dietze et al., 2022), the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) and the short version of Beck's Depression Inventory (BDI, Beck et al., 2013) were conducted in the subacute and chronic phase, to screen for mild cognitive impairment or dementia and to quantify the severity of possible depression. From the original group of patients described in Dietze et al. (2022), three were excluded due to MoCA scores of 17 or lower. None of the participants in the subacute and chronic phase measurements obtained such low scores.

2.4 Magnetic resonance imaging

Lesion location and lesion volume were extracted from magnetic resonance imaging (MRI) obtained on average 2 days after stroke, as explained in Dietze et al. (2022). In summary, after brain-extraction, linear registration to the structural template, provided by the Montreal Neurological Institute (MNI 152) was performed for the fluid-attenuated inversion recovery images and the lesion masks. Finally, we checked for possible overlap of the MNI-registered stroke lesions with brain areas belonging to the auditory pathway.

2.5 Psychoacoustic experiments

Custom Matlab scripts using the psychophysical measurement package AFC (Ewert, 2013), were used to generate and reproduce the stimuli. Closed headphones with passive sound attenuation (HDA300, Sennheiser electronic GmbH, Wedemark, Germany), driven by an external sound card (UR22mkII, Steinberg Media Technologies

GmbH, Hamburg, Germany) were used for all psychoacoustic experiments, with the exception of audiometric testing in the chronic phase. For these measurements, the system specified in section 2.5.1 was used.

2.5.1 Audiometry

Identical to the acute phase measurements described in Dietze et al. (2022), starting with the left ear, pure-tone audiometric thresholds were also measured in the subacute phase for a restricted set of frequencies (500 Hz, 1,000 Hz, 3,000 Hz). The same hardware as for the other experiments (see section 2.5) was used. In the chronic phase measurement, a clinical pure-tone audiometric air-conduction test ranging from 125 Hz to 8,000 Hz, starting with the right ear, was performed (Equinox 2.0, Interacoustics, Middelfart, Denmark).

The pure-tone average over the three frequencies 500 Hz, 1,000 Hz, and 3,000 Hz was calculated individually for the left ear (PTA3 L) and right ear (PTA3 R) and averaged (PTA3). To estimate the asymmetry of pure tone hearing loss, the difference between left and right PTA3 (PTA3 asymmetry) was calculated.

2.5.2 Tone-in-noise detection

The tone-in-noise detection experiment was conducted as described in Dietze et al. (2022): "The participants were presented with three intervals containing 500-ms bursts of octave-wide white noise centered around 500 Hz (333 Hz – 666 Hz). The stimuli were gated with 20-ms raised cosine onset and offset ramps. The intervals were separated by 300-ms silent gaps. In one of the three intervals, an additional 500-Hz pure-tone of 420 ms duration was added and temporally centered in the noise. The tone had the same ramp parameters as the noise, but its onset was 40 ms later than the noise. Similarly, the tone offset was 40 ms before the noise offset. The participants' task was to detect the deviating interval (the one containing the tone) and to press key number '1,' '2,' or '3' on a computer keyboard, indicating whether the first, second, or third interval was the odd one. The tone was either interaurally in phase with the noise (condition N_0S_0) or had an interaural phase difference of π (condition N_0S_π). The experiment started without any training and with two runs of the N_0S_π condition. This was followed by one run of the N_0S_0 condition. The noise was presented with 60 dB sound-pressure level (SPL). The level of the tone was initially 65 dB SPL in the N_0S_0 condition and 50 dB SPL in the N_0S_π condition. The level varied according to a one-up, three-down procedure, with a step size of 4 dB up to the second reversal, and a step size of 2 dB for the remaining 8 reversals, converging to 79.4% correct thresholds. Thresholds are calculated as the average of the last 8 reversals. If the staircase track hit the maximum tone level of 80 dB SPL during a measurement, re-instructions on how to perform the task were provided. If this did not lead to improvements in task performance, the run was stopped and marked as invalid. No feedback was given during the runs. The binaural masking level difference (BMLD) was calculated from the threshold difference between N_0S_0 and the better of the two N_0S_π runs."

2.5.3 Lateralization

The lateralization task and the calculation of variables for quantitative description of the lateralization pattern were also carried out as reported in Dietze et al. (2022): "For the lateralization task, again, a one-octave wide white noise, centered around 500 Hz with an interaural difference in either level or time was presented. The stimuli were generated by copying the same noise sample to both channels and then applying the interaural difference in time or level. The task was to indicate where the sound was perceived inside the head. Responses were given by pressing one of the horizontally aligned numbers '1' to '9' on a computer keyboard, above the letter keys. The participants were instructed to press '1' when the sound was heard on the very left side of their head, '5' for sounds perceived in the center of the head and '9' for the very right side. For possible intracranial positions between the center and the two extremes, the participants were asked to press the respective number '2,''3,''4,''6,''7' or '8' on the keyboard. For visual guidance, a template with a schematic drawing of a head indicated the positions of the ears and the center relative to the response buttons. The template covered all of the keyboard except for the numbers '1' to '9.' The duration of the stimuli was 1 s, gated with cosine ramps of 10 ms duration and presented at 70 dB SPL. ITDs ranging from −600 µs to 600 µs in steps of 200 µs, and two ITDs outside the physiological range (−1,500 µs and 1,500 µs), were presented. The ILDs ranged from −12 dB to 12 dB in steps of 4 dB. The level of the left- and right-ear signals was changed without changing the overall energy by applying the formula presented in Dietz et al. (2013). In addition, monaural stimulation of the left ear and right ear was tested in the lateralization task. Each stimulus was presented six times in random order. The diotic stimulus (zero ITD/ILD) was presented eight times. To ensure one common reference system for both types of interaural differences, ILD and ITD stimuli were presented interleaved. In contrast to the investigations by Furst et al. (2000), no training and no center reference were provided in our study. The response to the first trial of each stimulus was not used in further analyses.

Several variables for quantitative description of the lateralization pattern were calculated:

A linear fit to the three left-favoring and right-favoring stimuli, individually for ILD stimuli (−12 dB, −8 dB, −4 dB and 4 dB, 8 dB, 12 dB) and ITD stimuli (−600 µs, −400 µs, −200 µs and 200 µs, 400 µs, 600 µs) was used to describe the steepness of the participants' lateralization percept (*ILD L slope, ILD R slope, ITD L slope, ITD R slope*). The logarithmic ratio of the left and right slope (*ILD slope ratio, ITD slope ratio*, e.g., *ILD slope ratio = log(ITD slope L / ILD slope R)*) indicates an asymmetric steepness of the two sides.

Variables that inform about side biases in the responses were calculated: The mean of the responses to all ITD or all ILD stimuli (*ITD mean, ILD mean*) and the mean of the fit to left-favoring and right-favoring stimuli (*ITD L fit, ITD R fit, ILD L fit, ILD R fit*) were calculated. Furthermore, the mean of those stimuli that were perceived as being in the center of the head (when key '5' was pressed), was calculated for ILD and for ITD stimuli (*ITD center, ILD center*). The so-called *diotic percept* was the mean of the responses given for the zero ILD/ITD stimuli.

Another feature of the lateralization data is its variability. For this, the standard deviation for zero ILD/ITD was calculated (*diotic std*), as well as the mean of the standard deviations of the responses to each ILD stimulus (excluding the monaural stimulation, *ILD std*), each ITD stimulus (*ITD std*) and the mean standard deviation of the left-favoring and right-favoring stimuli independently (*ITD L std, ITD R std, ILD L std, ILD R std*). Their logarithmic ratios (*ITD std ratio, ILD std ratio*) can indicate differences in the variability of left-favoring and right-favoring stimuli.

The maximal range of lateralization was calculated by the difference of the maximally lateralized responses given for ITDs within the physiological range (*ITD range*), and for all ILDs excluding monaural stimulation (*ILD range*). The logarithmic ratio of the ranges obtained with ILD and ITD stimuli (*range ratio*) informs about differences in the ranges perceived using the two types of stimuli.

The perception of the monaural left and right (*mon left, mon right*), and the ITDs of ±1,500 µs (*neg 1,500, pos 1,500*) was only evaluated in terms of the mean response to these stimuli […].

Whenever values of the calculated variables are reported, they are in the unit of response keys (a difference of one response button corresponds to 1/8 of the distance between the two ears), except for the variables describing the goodness of fit and the ratios."

For each of the variables, a normal range was defined as follows: The values obtained from the 12 control subjects were sorted in ascending order. Whenever a patient's value for a variable fell within the range of the second to the eleventh value of the control group, this value was considered normal, and values outside these limits were marked as divergent. On average, divergences from the normal range can be expected in 5 of the 31 variables even in a normally performing participant, since 2/12 or 16.67% of the control group's values are outside the normal range by definition. Participants with no more than five divergences from the control group are therefore defined as having normal lateralization.

To quantify the change in lateralization performance, the change in each of the lateralization metrics from one phase to the other is expressed in units of standard deviation of the respective metric in the control group. Positive changes are those where the metric values in the later measurements approach the mean of the control group, and negative changes are those where the metric values in the later measurements diverge more from the control group's mean.

2.6 Statistical analyses

The control group and the three measurement phases each contained different and rather small numbers of participants. For this reason, and because the values were not all normally distributed, nonparametric tests were mainly used to test for the different effects: The Kruskal-Wallis test was followed by Dunn's multiple comparison test as a post-hoc test for the analyses of the general assessment results reported in Section 3.1. Kruskal-Wallis tests were also performed to compare the binaural masking level differences between the groups and the number of divergences in the lateralization task in Sections 3.3 and 3.4.2. Correlations were calculated using Spearman's correlations as described in Section 3.4. Statistical analyses of the audiometric results presented in Section 2.5.1 were performed using repeated measures analysis of variance (ANOVA) and Student's *t*-test, as all requirements for parametric testing were met.

3 Results

3.1 General assessment

Mean values and standard deviations of the non-auditory testing and the audiometric results of the control group and the stroke groups at the three measurement phases (acute, subacute, and chronic) are shown in Table 1. Test statistics of the Kruskal-Wallis Test are reported in the rightmost column of Table 1. The test revealed that only the score of the cognitive screening test (MoCA) differed significantly between the groups (small effect, $\eta^2 = 0.19$), but age, hearing thresholds (PTA3, PTA3 asymmetry), and the score of the depression screening (BDI) scores did not differ. According to Post-Hoc testing with the Dunn's test, the control group's MoCA scores differed significantly from the patients' MoCA scores in the acute phase ($z = -4.16$, $p < 0.001$), subacute phase ($z = -3.55$, $p < 0.001$), and chronic phase ($z = -2.53$, $p = 0.011$), but there were no significant differences between the scores of the three phases.

3.2 Audiometry

The results of the audiometry are shown in Figure 1. The PTA3, calculated over the three frequencies for each of the three measurements, showed that the pure-tone hearing thresholds were comparable for the three measurement phases and the two audiometric measurement procedures. A PTA3 of 20 dB HL or higher was reached in 39, 35, and 38% of the patients in the acute, subacute, and chronic phase measurements, respectively. Only taking the 15 patients that participated in all three measurements into account, a repeated measures ANOVA revealed no significant effect of the three measurement phases (acute, subacute, chronic: $F(2, 28) = 1.82$, $p = 0.18$, $\eta^2 = 0.007$) or side (left, right: $F(1, 14) = 0.32$, $p = 0.58$, $\eta^2 = 0.001$), nor an interaction of measurement phase and side on those participants' PTA3 ($F(2, 28) = 2.52$, $p = 0.09$, $\eta^2 = 0.004$).

In panels A-C of Figure 1 patients with higher values (i.e., worse hearing thresholds) in the left compared to the right ear are represented within the blue triangle and higher thresholds in the right compared to the left ear within the red triangle. It can be seen that in all three measurement phases there is a statistically insignificant trend toward worse hearing thresholds for the first ear measured (left ear in acute and subacute phase, right ear in chronic phase; acute: $t(30) = 1.55$, $p = 0.13$, subacute: $t(23) = 0.57$, $p = 0.57$, chronic: $t(21) = -0.07$, $p = 0.95$).

A comparison of the PTA3 of the acute phase measurement and the last measurement is presented in Figure 1D. Values within the red triangle represent those patients with worse hearing thresholds in the acute compared to the later phases and values within the orange triangle represent those patients with worse thresholds in the last compared to the acute phase measurement. Only for a few patients (S10, S20, S23, S26, and S48) did the PTA3 of the two measurements differ by more than 5 dB. Of these five individuals, two had improved and three had deteriorated hearing thresholds. In general, no significant difference in hearing thresholds of the acute and the last measurement were observed ($t(30) = -0.70$, $p = 0.49$).

3.3 Tone-in-noise detection

In the acute phase measurements, 29 of 31 stroke patients produced valid tracks in both conditions of the tone-in-noise detection task (N_0S_π and N_0S_0), allowing the BMLD from the difference between the N_0S_π and N_0S_0 thresholds to be calculated. The same was true for 11 of the 12 control subjects, 23 of 24 patients in the subacute and all 22 patients in the chronic phase. Of those patients with invalid

TABLE 1 General assessment results.

	Control $N = 12$	Acute $N = 31$	Subacute $N = 24$	Chronic $N = 22$	Test statistics
Age [years]	61.5 (9.3)	62.0 (20.0)	58.0 (15.0)	70.5 (16.5)	$\chi^2(3) = 2.83$, $p = 0.418$
PTA3 [dB HL]	13.8 (14.0)	17.5 (9.0)	18.0 (8.4)	15.0 (15.1)	$\chi^2(3) = 3.25$, $p = 0.354$
Absolute PTA3 asymm. [dB]	2.6 (8.5)	0.8 (4.2)	1.5 (5.8)	−0.3 (4.9)	$\chi^2(3) = 4.22$, $p = 0.239$
MoCA score	29.0 (1.5)	24.0 (4.0)	25.0 (4.5)	27.0 (2.0)	$\chi^2(3) = 18.86$, $p < 0.001$
BDI short score	4.0 (5.1)	6.5 (5.1)	6.5 (5.1)	6.5 (5.1)	$\chi^2(3) = 4.93$, $p = 0.177$

Median and interquartile ranges for the control group and the patients in the acute, subacute, and chronic phases of stroke and the Kruskal Wallis test statistics. PTA3, pure tone average: average hearing thresholds for 500, 1,000, and 3,000 Hz; MoCA, Montreal Cognitive Assessment; BDI, Beck's Depression Inventory. Values are given in the form "median (interquartile range)".

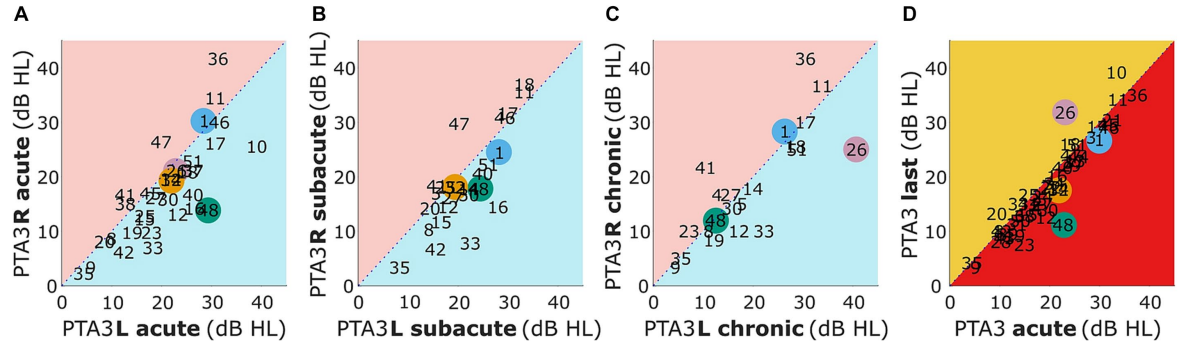

FIGURE 1
Mean pure-tone audiometric thresholds for 500, 1,000, and 3,000 Hz for the left (PTA3 L) vs. right (PTA3 R) side for the acute, subacute, and chronic phase **(A–C)** and for acute vs. last measurement **(D)**. Selected patients are highlighted by the color coding used throughout the figures (S1 = blue, S26 = pink, S32 = orange, S48 = green).

tracks in the acute phase measurement, S20 participated again in the subacute phase and S18 in the subacute and chronic phase. In the later measurement, S20 had a BMLD of 12 dB. S18 did not produce valid tracks in the subacute phase, but had a BMLD of 15 dB in the chronic phase measurement.

The normal values of BMLD, as defined by the second up to the n-1 highest values of the valid control group results, ranged from 7.5 dB to 18.5 dB. Of those participants that produced convergent tracks, a BMLD of 7.5 dB or more was measured in 27 of 29 patients in the acute phase, in all 24 patients in the subacute phase, and 21 of 22 patients in the chronic phase (see Figure 2). A Kruskal Wallis test revealed that there is no significant effect of the four groups (control, acute, subacute, chronic) on the participants' BMLD values ($\chi^2(3) = 0.17$, $p = 0.982$).

3.4 Lateralization

All control subjects and all patients completed the lateralization task in each of the measurements in which they participated. Normal lateralization (with no more than five divergences from the control group) was found for 16% of the patients in the acute, 18% in the subacute, and 4% in the chronic phase of stroke. The lateralization patterns of four selected patients (details are given in Figure 3A and Table 2) are shown in Figures 3B–E. These patients were selected, because they represent well the variety of lateralization patterns and their changes from the acute phase to the later phases. Patients that show recovery of lateralization performance are shown as well as patients showing deteriorating lateralization. Notice, that three of the four patients had lesions in the right hemisphere only. More details can be found in Section 3.4.1. The lateralization results of all other participants can be found in the Supplementary Data.

Across the three measurement phases, the metric 'diotic percept' that is associated with a spatial percept away from the auditory midline for stimuli without any ILD or ITD is positively correlated with the asymmetry of PTA3 as tested with Spearman's rank correlation test ($\rho = 0.306$, $p = 0.007$).

3.4.1 Single-patient observations

Patient S1 (81 years) had multiple lesions in the right hemisphere, including the occipital lobe, lingual and fusiform gyrus, hippocampus, thalamus and the corpus callosum, with a total lesion volume of 6.5 cm^3 (see Figures 3A,C and Table 2). As shown in Figure 3C, the lateralization pattern was very close to the control group in the acute phase, becoming more variable in the subacute phase. In this phase, there were left–right confusions for physically right-leading, but less for left-favoring stimuli for ILD and ITD stimuli. A slight shift toward the right side can be observed in the subacute and chronic phases. The hearing thresholds at the right ear for 500 Hz were worse by 6 dB in the chronic phase but were within normal limits for the other frequencies and other measurement phases.

In Figure 3B, side-oriented lateralization with both ILD and ITD cues in the acute phase measurement can be seen for patient S32 (75 years) who had a lesion in the right pons (total lesion volume:

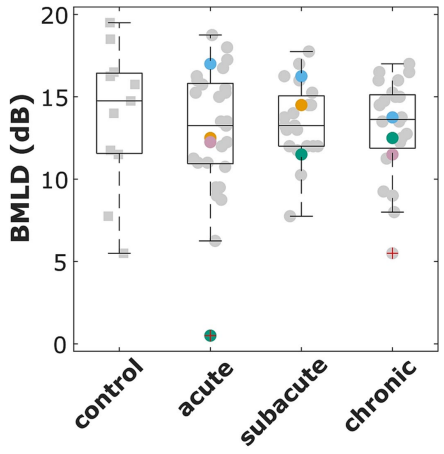

FIGURE 2
Binaural masking level difference (BMLD) for the control group and all patients that participated in the acute, subacute, and chronic phase measurements. The red cross indicates outliers (i.e., more than 1.5 times the standard deviation outside the quartile boundaries). Selected patients are highlighted by the color coding used throughout the figures (S1 = blue, S26 = pink, S32 = orange, S48 = green).

0.6 cm^3, covering parts of the primary auditory pathway, see Figures 3A,B and Table 2). The stimulus was perceived close to the ears even for small ILDs or ITDs, with a few left–right confusions for physically left-favoring stimuli. Both stimuli with unnaturally large ITDs (±1,500 μs) were perceived on the left side. In the subacute phase, the lateralization pattern resembled the control group in most aspects, including the +1,500-μs stimulus now being perceived on the leading right side. This patient's pure tone audibility stayed constant over time, with no strong asymmetry between left and right ear thresholds.

Patient S26 (77 years, see Figures 3A,E and Table 2) had several lesions in the right hemisphere, including sulcus intraparietalis, superior temporal lobe, and anterior insula and a lesion in the dorsal left medulla oblongata (total lesion volume: 0.6 cm^3). As in patient S32, this patient showed side-oriented lateralization patterns for ILD and ITD stimuli in the acute phase, but did not recover to normal lateralization in the later measurement (chronic phase). Instead, a shift of lateralization toward the right side was observed. Importantly, the pure-tone hearing thresholds of this patient were symmetric in the acute phase, but asymmetric in the chronic phase measurements, with the PTA3 of the left ear being 14 dB worse than for the right ear, but with no asymmetry at 500 Hz. Interestingly, all stimuli with ILDs (favoring either the left or the right ear) were perceived on the right side, whereas the ITDs of −400, −600, and − 1,500 μs were frequently perceived on the leading left side.

Marked changes in the lateralization pattern from the acute to the subacute and chronic phase can be seen in patient S48 (74 years, see Figures 3A,D and Table 2). This patient had multiple lesions in the right hemisphere in the medial and superior frontal lobe, precentral gyrus, and several smaller right-sided white-matter lesions. The total volume of all lesion sites was 11.9 cm^3. High variability for individual responses, especially to physically left-favoring stimuli, and a shift of the responses toward the right side were observed in the acute phase. In the subacute phase, the responses were much less variable, and all left-favoring ILD, but not ITD stimuli, were perceived in the center of the head. Finally, in the chronic phase, the responses were again more variable, but overall not diverging much from the control-group behavior. This patient's PTA3 was asymmetric in the acute phase (13 dB worse in the left ear), but this was reduced to 4 and −2 dB in the subacute and chronic measurements, respectively, because of an improvement of the left ear PTA3.

3.4.2 Differences to the control group across measurements

The absolute number of divergences from the control group in the lateralization metrics (described in section 2.5.3) is shown for all patients in Figure 4. Values on the diagonal represent patients with the same number of divergences in two measurements (see patient S25 in panel A), whereas numbers below the diagonal represent patients with a smaller number of divergences in the later stages. Summed over all three comparisons, slightly more patients are on or below the diagonal (stable or improved lateralization) than above the diagonal (deteriorated performance) with 32 cases of no change or improvement vs. 26 cases of deterioration.

A Kruskal Wallis Test was done to estimate the effect of the measurement phase on the number of divergences. It revealed no statistically significant effect of the three measurement phases (acute, subacute, chronic) on the number of divergences from the control group ($\chi^2 = 1.62$, $p = 0.444$).

When comparing the changes from one phase to another as indicated by the circle and diagonal error bars (mean and standard deviation) in Figure 4, one can see that the variability across patients is reduced for the subacute vs. chronic measurement, whereas the mean values remain unchanged. The latter observation is confirmed by the missing effect in the Kruskal Wallis test done on these three distributions of changes ($\chi^2 = 1.2$, $p = 0.549$).

Divergences in the individual metrics for each patient and the three measurement phases can be found in the Supplementary Figures S1–S3. The lateralization performance of the patients S1, S26, S32, and S48 was described in Section 3.4.1 on the basis of visual inspection. These observations are also reflected in the number of divergences shown for these color coded patients in Figure 4.

3.4.3 Changes in lateralization patterns across measurements

To be able to follow the changes in lateralization abilities across the measurement phases, we calculated the difference of the lateralization metrics in units of interquartile range of the control group across the measurements. In Figure 5 the metrics given in the columns are clustered in group A to group F, representing changes in the lateralization pattern (A: shift of the auditory space, B: variability of the data, C: slopes of the fits, D: perceived ranges, E: perception of monaural stimuli, F: ITDs outside the physiological range). Each row represents the changes in the respective metrics for one patient. The patients are grouped according to the lesion locations (e.g., S32 belongs to the brainstem right (bs r) lesion group). It became clear that in the later measurement phases, some participants' lateralization approached closer to normal behavior (i.e., the mean lateralization metric values of the control group) with respect to many metrics. For others, in the later measurements many metrics diverge even further

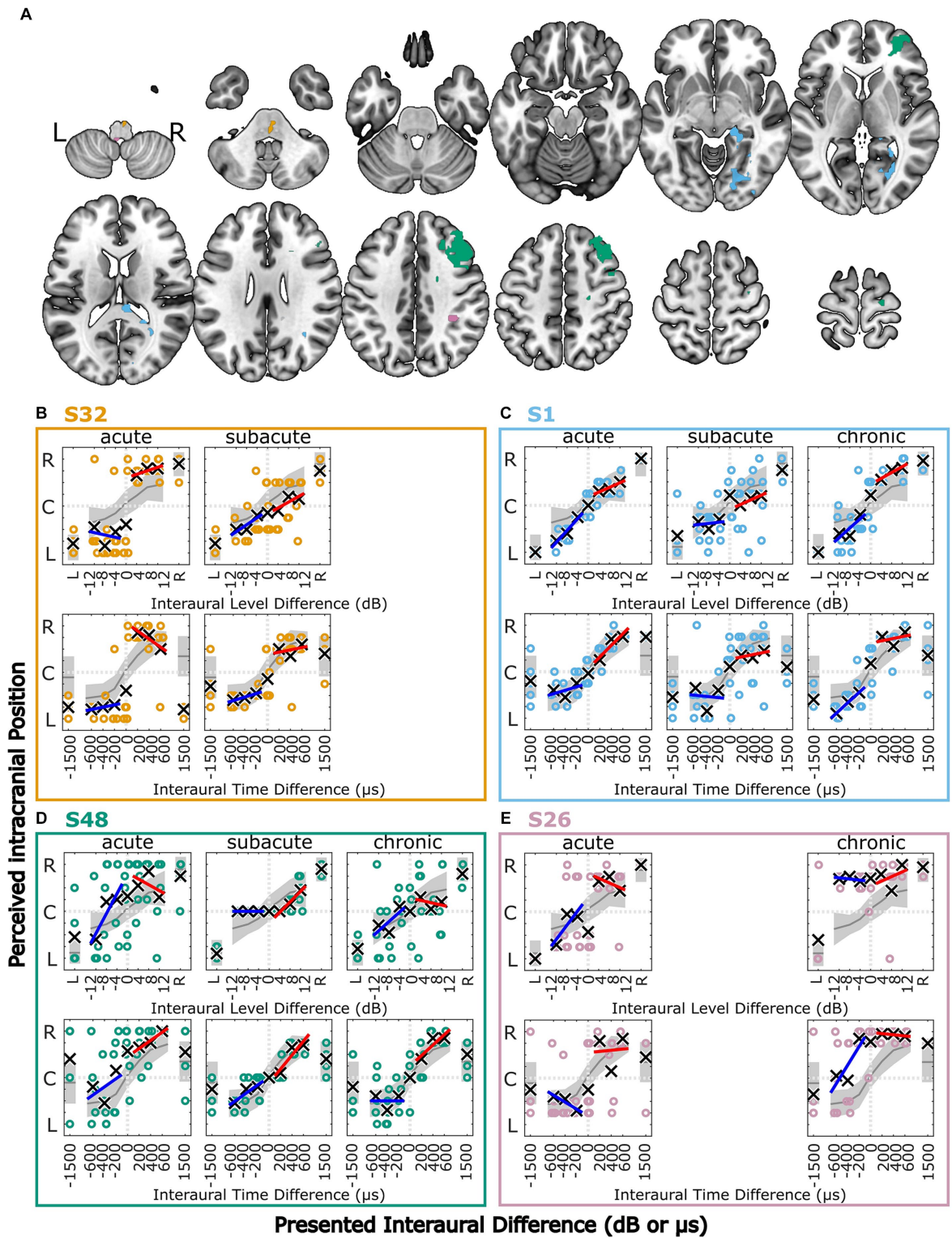

FIGURE 3
Lesion locations for four selected stroke patients overlaid on axial slices of the MNI152 template **(A)**. Lesion group, lesion volume and additional information is given in Table 2. **(B–E)** Results of the lateralization task for four selected stroke patients in the three measurement phases. The colored symbols represent the responses given to the individual trials of the same stimulus, except for the discarded first trial. The black crosses indicate the means of the given responses. The red and blue lines represent linear fits to right-favoring and left-favoring stimuli, respectively. The gray line and shaded area indicate the mean and the 1.5 times standard deviation interval around the mean response of the control subjects. Selected patients are highlighted by the color coding used throughout the figures (S1 = blue, S26 = pink, S32 = orange, S48 = green).

TABLE 2 Additional information for the four selected stroke patients.

Patient ID; age	Lesion group; lesion volume	PTA3; asymmetry [dB HL]	Thr 500 Hz; asymmetry [dB HL]	MoCA score	Number of divergences
S32; 75 years	Brainstem right; 0.6 cm^3	20, 18, –; 0, −1, –	21, 19, –; −3, 3, –	22, 24, –	21, 8, –
S1; 81 years	Multiple lesions right; 6.5 cm^3	29, 26, 27; −3, 3, −3	15, 17, 16; 0, 0, −6	20, 21, 20	6, 15, 13
S48; 74 years	Multiple lesions right; 11.9 cm^3	21, 20, 11; 13, 4, −2	18, 15, 3; 9, 1, 5	22, 22, 23	22, 11, 9
S26; 77 years	Multiple lesions bilateral; 0.6 cm^3	21, –, 32; 0, –, 14	13, –, 20; 0, –, −1	24, –, 27	17, –, 21

PTA3, pure tone average: average hearing thresholds for 500, 1,000, and 3,000 Hz; Thr 500 Hz, hearing threshold at 500 Hz; MoCA, Montreal Cognitive Assessment. For "PTA3," "Thr 500 Hz," "MoCA score" and the "Number of Divergences" the three entries represent values for the acute, subacute, and chronic phase, respectively. Missing values are indicated by "–".

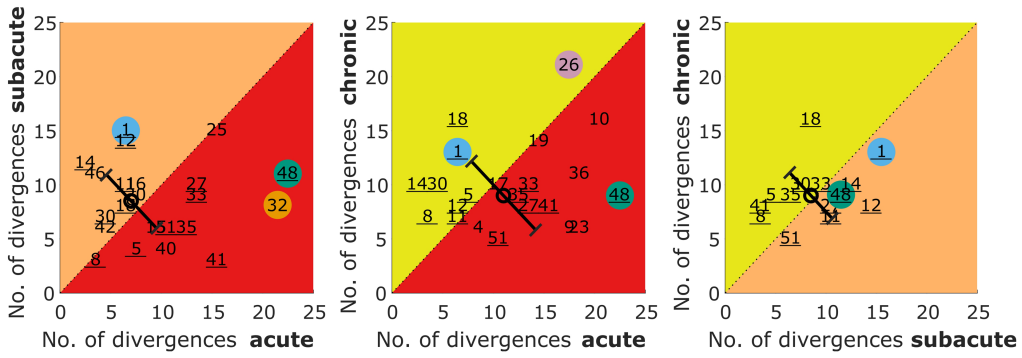

FIGURE 4
Number of divergences from the control group in the lateralization task for acute vs. subacute, acute vs. chronic, and subacute vs. chronic phase. The number refers to the patient identifier, with the number of those patients that participated in all three measurements being underlined. Selected patients are highlighted by the color coding used throughout the figures (S1 = blue, S26 = pink, S32 = orange, S48 = green). The circles represent the mean of the patients and the error bars show the standard deviation of the change in the number of divergences from one to the other phase.

from the control group (see in Figure 5 the blue and red squares for improved and deteriorated metric values, respectively).

A further examination of the example patients S1, S26, S32, and S48 revealed that the changes in their lateralization performance as described before on the basis of visual inspection of Figure 3 is reflected in the quantitative analyses presented in Figure 5: For patient S1, the temporary increase in variability in the subacute phase and the shift toward the right side that was observed in the subacute and chronic phases, is clearly reflected in the high number of deteriorated values in the respective clusters B and A in Figures 5A–C. The improvements in the lateralization performance of patient S32 can be clearly observed in Figure 5A. Changes toward normal lateralization were found in cluster A, associated with shifts of the auditory space and in the metrics of the ±1,500-μs stimuli (cluster F). The only marked change toward poorer metric values is present in the variability of right-sided ILD stimuli. For patient S26, a strong shift toward the right side is reflected in Figure 5B in the change of the metrics in cluster A (associated with shifts). Since physically left-leading ITD stimuli were not always shifted to the right side, the slope of these stimuli recovered relative to the acute phase, as seen in the positive change of ITD L slope. For patient S48, the observation of improved performance, especially with regard to variability and shift in the later stages, is reflected in Figures 5A,B. In panel B, the metric 'ILD std. ratio' and the mixed effects in panel Figure 5C reveal the strong difference in the perception of left-and right-favoring ILD stimuli in the subacute phase.

In contrast to the absolute numbers of divergences as shown in Dietze et al. (2022) and Supplementary Figures S1–S3, the patients' changes in lateralization patterns are not consistent within lesion groups. This can be seen in Figure 5 from the fact that within one lesion group the strongest changes are not only found within one metric group (i.e., darkest squares occurring distributed over groups A to F), nor is the trend of the changes toward one direction (i.e., blue and red squares). However, individual patients recovered especially with respect to one cluster of metrics, but showed poorer lateralization metrics in another cluster of. One such example is patient S25, who had improved values in the metrics related to variability (cluster B) from the acute to the subacute phase, while showing poorer values for the metrics related to a shift of the auditory space (cluster A). The exact opposite behavior to S25 was shown by in S48. Obviously, only those metrics that were far from normal values in the first measurement phase can change by a large amount in the later measurements.

4 Discussion

The aim of this longitudinal study was to quantify the effects of ischemic stroke on binaural perception in a population of patients with only mild symptoms of stroke and with different lesion locations from the acute, to the subacute and the chronic phase of stroke. We hypothesized that binaural performance recovers toward later measurements.

In our population, binaural unmasking, assessed with a dichotic tone-in-noise detection experiment was not substantially affected by ischemic stroke and was constant over the measurement phases. For

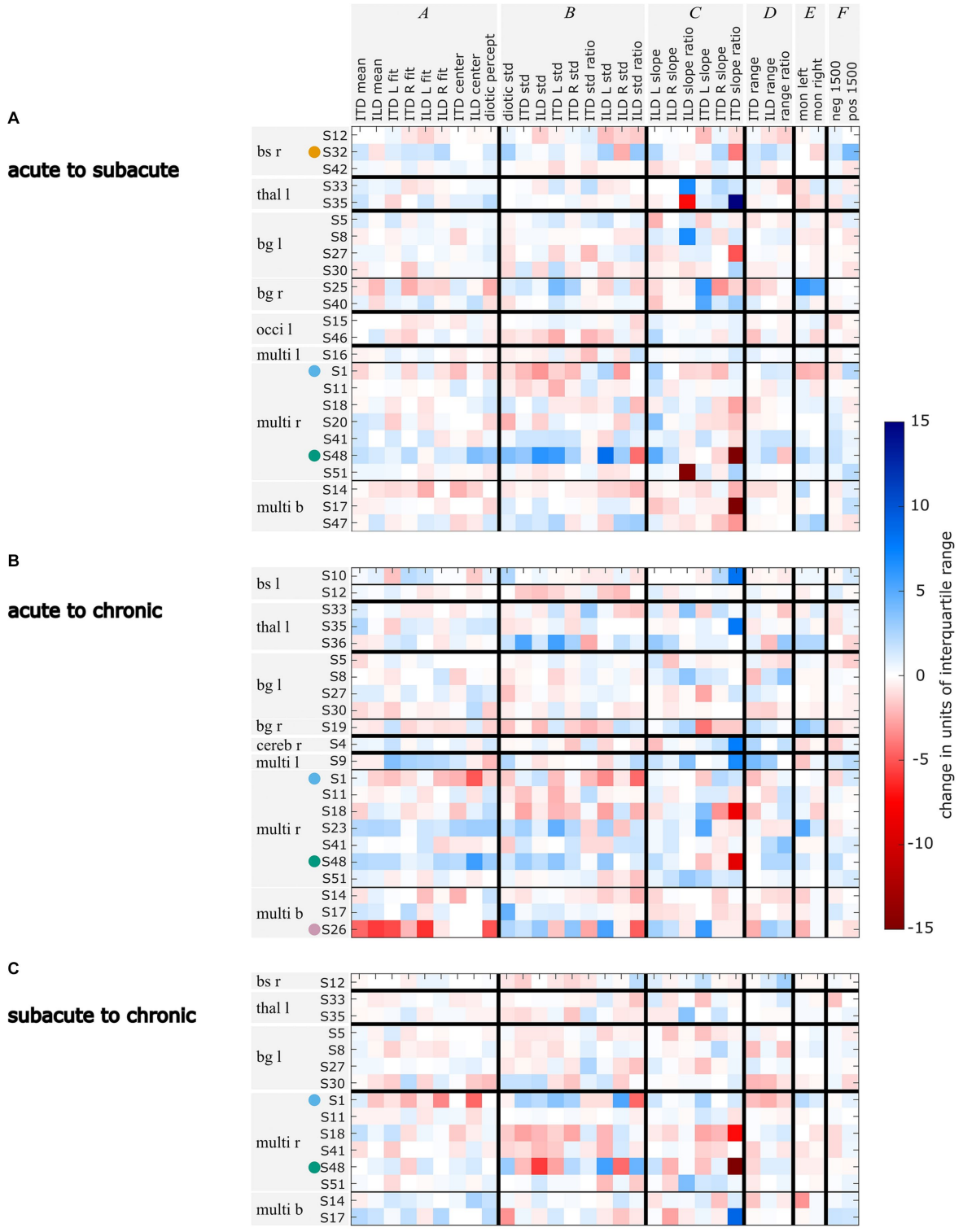

FIGURE 5
Changes in units of standard deviation of the control group for each lateralization metric for the comparisons acute vs. subacute **(A)**, acute vs. chronic **(B)**, and subacute vs. chronic **(C)**. Changes that lead to the metric values being further away from the control group's mean are marked in red, changes that lead to metric values becoming closer to the control group's mean are marked in blue. Selected patients are highlighted by the color coding used throughout the figures (S1 = blue, S26 = pink, S32 = orange, S48 = green). The patients are grouped by their lesion site with bs = brainstem, thal = thalamus, bg = basal banglia, occi = occipital lobe, multi = multiple lesion sites and referring to the lesion side with r = right, l = left, and b = bilateral.

many patients, in contrast, the lateralization patterns differed from the control group in the acute phase of stroke. Toward the later measurements, many patients showed recovery of their lateralization abilities. When comparing the number of divergences in the acute to the chronic phase, eleven patients showed recovery of their lateralization abilities, which is in line with our hypothesis. This is comparable to other adaptive and maladaptive effects and to the spontaneous recovery observed after stroke as discussed in Cramer et al. (2011), and to the fast relearning of binaural hearing after alterations of binaural cues induced by a changed periphery (reviewed by Wright and Zhang, 2006). Recovery after stroke is linked to many factors, including experience. Butler (1987) showed that after altering the interaural cues, only those acoustic features that the participants had training in were relearned. Since this was not part of our investigations, we do not know how the patients behaved between the measurements, and the extent to which they trained everyday sound-source localization situations.

A slightly smaller group of patients' lateralization performance deteriorated over time. When comparing the number of divergences in the acute to the chronic phase, nine patients showed deteriorated lateralization performance in the later phase. Deteriorated performance could be explained by secondary cell death of synaptically deprived brain areas, as suggested by Kolb and Teskey (2012). It could be also due to the imbalance of neuronal activity in the two hemispheres with hyperactivity in the contralesional hemisphere that could, in turn, further suppress the lesioned hemisphere by callosal inhibition and may reflect mal-plasticity, as suggested by Thompson et al. (2012). Further, it is possible that these patients suffered another, but clinically silent stroke after the acute phase measurements causing stronger or additional difficulties with binaural hearing tasks. Especially within the first year after first-time stroke, patients have a high risk of recurrent stroke (Burn et al., 1994).

Binaural hearing difficulties observed in the acute phase measurements (see Dietze et al., 2023) were partially consistent within lesion groups. In contrast, the recovery of binaural hearing observed in this study is not consistent within lesion groups. From each lesion group, some patients showed long-term recovery, whereas others' lateralization patterns worsened.

4.1 Single-patient observations

In patient S32, lesions in the right pons, including parts of the auditory pathway, appear to have caused binaural hearing impairment. These divergences from the control group are expected because the first stages of binaural interaction are located in the pons. Side-oriented lateralization patterns were also reported by Furst et al. (2000) in patients with lesions rostral to the superior olivary complex. However, we do not know whether the patient perceived one fused auditory image or two separate stimuli due to lack of binaural fusion.

Patient S1 showed ipsi- and contralesional impairments following right-sided lesions, in line with the findings of Spierer et al. (2009). The lesion also involved parts of the thalamus. Patients with such lesions have previously been reported to show shifts of the auditory space (Dietze et al., 2022). In this particular patient, it is unlikely that the shift of auditory space was caused by hearing threshold asymmetry, because the patient had worse hearing thresholds in the right ear, but the shift was toward the right side. Intuitively, one would expect stimuli to be perceived closer to the better-hearing ear.

According to the mapping of the MRI data onto standard templates, the lesions of subject S26 did not involve any part of the auditory pathway. However, the right temporal lobe and insula as well as the left medulla have previously been reported to be involved in spatial hearing (e.g., Sanchez-Longo and Forster, 1958; Aharonson et al., 1998; Bellmann et al., 2001) and seemed to cause binaural hearing difficulties in this patient as well. The deterioration of the lateralization pattern observed in the chronic phase could be attributed to worse high-frequency hearing thresholds in the left compared to the right ear in this patient. Interestingly, while all stimuli including an ILD were perceived on the right side, even small left-leading ITDs caused some of the stimuli to be perceived on the left side.

The most severe lateralization difficulties of the four example subjects were observed in subject S48 with multiple right-sided lesions in the cortex and white matter. In this patient, the most peculiar difficulties are those observed for ILD stimuli in the subacute phase: While normal lateralization occurred for right-leading stimuli, all left-leading ILD stimuli were perceived in the center of the head without any exception. None of the hearing threshold-related measures could explain these observations.

4.2 Confounding factors and limitations of the study

Studies in clinical populations pose simultaneous advantages and disadvantages (Gallun, 2021). A large number of participants can be measured when the experimental paradigm is adjusted to be as short as possible. Valuable information on the abilities of patients with clinically manifested impairments can be obtained, but is confounded by many factors. Even though we assessed the pure-tone hearing thresholds and cognitive state of the patients, these are possible confounding factors whose influence cannot be removed from the results. Hearing loss, and especially asymmetric hearing loss, poses challenges to interpreting the lateralization patterns. Hearing-threshold asymmetry was correlated with lateralization metrics associated with shifts of the lateralization pattern. The percentage of variance explained by this correlation is 9%. However, it was not part of our measurements to assess the causes of the participants' hearing loss. It is also not clear how the general state of the participants differed across the three measurements, but with the lateralization patterns being worst in the acute phase, their cognitive capacities measured with the MoCA test were also lowest at this measurement. According to the NIHSS items on visual neglect and the Star Cancelation Task, none of the patients showed signs of visuo-spatial neglect in the acute phase. Thus, cognitive impairment due to multisensory neglect as discussed in Pavani et al. (2004) is presumably not causing lateralization difficulties in the stroke population of the present study. On the other hand, the motivation to participate in the study might have differed for the three measurement phases for each patient individually and was not assessed. The high dimensionality of this data set and the variety of lesion locations, hearing losses, and cognitive capacities, complicate the interpretation of the data. Yet even in the chronic phase, 6 of 22 patients still clearly showed impaired binaural abilities (at least 8 divergences from the control group), despite mild or absent clinically registered symptoms of stroke.

The acute phase measurements of this study were carried out on 50 patients, but only a subset of them participated again in the later measurement phases. Consequently, the number of longitudinally assessed patients was reduced to 31 who participated in more than one measurement. Although this number of participants is comparable even to other single-appointment studies on this topic (e.g., 21 in Bamiou et al., 2012; 22 in Aharonson et al., 1998; 50 in Spierer et al., 2009), it is a limitation. With more participants, the different lesion-location groups could be better represented, and confounding factors would be more evenly distributed across these groups.

4.3 Advantages of cue-specific experiments

As mentioned above, re-learning to use altered binaural information relies on exposure to the specific acoustic features (Butler, 1987). ILD or ITD cues in isolation are not present in real-life listening scenarios. Instead, each cue is accompanied by the matching other cue as well as by spectral information. In the frequency range of the stimuli used here (centered at 500 Hz), listeners usually rely on ITD-cues, whereas for far-field sources, ILDs are negligible at these low frequencies (Strutt, 1907). In the current study, one cue is always fixed at zero, while the other varies, resulting in artificial combinations of ITD and ILD. In some patients, we observed that the lateralization of ITD stimuli recovered better than the lateralization of ILD stimuli (e.g., S19, S25, S32, S36, S40). However, the opposite was also found in some patients (S19, S41). It is important to note that stimuli with ILD or ITD were presented in an interleaved fashion, ensuring that the same reference system was used.

We showed that headphone-based independent manipulation of interaural cues facilitates the detection of binaural-processing impairments that may remain undetected in localization (i.e., loudspeaker identification) experiments. This is most likely because real-world cues with high redundancy in the interaural cues are presented in localization tasks. After 40 years of research on cortical spatial maps, Middlebrooks (2021) concluded that unlike for other sensory modalities, no cortical spatial map exists for the auditory system. Instead, auditory space is represented by highly dynamic spatial neurons in the cortex (Middlebrooks, 2021). Consequently, it is possible that these neurons can react dynamically to altered binaural information, leading to a complete recovery of spatial hearing in free-field localization tasks, despite no recovery or even maladaptive effects for the artificial headphone-stimuli presented here. These stimuli are not externalized and not experienced in real-life listening scenarios, nor do they contain redundant information. Although more ecologically valid tasks can inform better about direct consequences in everyday life, cue-specific tasks as used in our study uncover difficulties in the underlying basic processing.

4.4 Relevance of binaural impairments to daily life

The benefits that arise from binaural hearing are undeniably important in everyday life (Avan et al., 2015), and binaural tests have been suggested to capture the variability across listeners with auditory difficulties that is not associated with classical monaural auditory tests such as pure-tone audiometry (Diedesch et al., 2021). Therefore, the influences of impaired binaural hearing are of relevance to anyone dealing with stroke. Affected individuals may or may not be aware of an existing impairment in binaural hearing. Patient-reported difficulties in spatial hearing after stroke were shown in Bamiou et al. (2012), whereas Javer and Schwarz (1995) reported that participants were not aware of their localization bias. The lack of awareness of one's own condition, referred to as anosognosia, including, but not limited to the phenomenon of neglect, is not assessed in this study. However, it is important to keep in mind that awareness of impairments can be crucial for save navigation in everyday life. Due to time limitations, we did not systematically investigate patient-perceived impairments.

We showed that some patients' ability to use binaural information for the lateralization task recovered, whereas for others no recovery was observed until the last measurement. In both groups, we can assume that capacities are spent on either adaptive processes or managing the impairments in daily life, resulting in a higher listening effort in situations where binaural hearing is exploited. The additional cognitive load caused by stroke-induced impairments in binaural hearing "can interfere with other operations such as language processing and memory for what has been heard" (Peelle, 2017).

At the same time, studies such as ours, that determine the conditions under which recovery of perception occurs, "can provide insight into the plasticity and structure of the underlying neural processes. They can also inform the extent to which, and how best, individuals with impaired sound-localization abilities can be aided through training." (Wright and Zhang, 2006). A study on the common stroke-induced phenomenon of neglect showed that deficits in spatial perception in different modalities were reduced by auditory spatial stimuli (Kaufmann et al., 2022). Rehabilitation training should therefore also rely on training in the auditory domain for relearning of auditory and non-auditory spatial perception, such as the positive effects of music listening on general recovery after stroke that were demonstrated by Särkämö et al. (2010). Carlile (2014) similarly pointed out the relevance of multi-modal training. He showed that compared to visual inputs, the involvement of the motor-state is even more important for the capacity to recalibrate to acoustic cues.

5 Conclusion

In this study, the effects of ischemic stroke on binaural perception were quantified using longitudinal measurements in the acute, subacute, and chronic phases of stroke in a population of patients having only mild symptoms and with different lesion locations. We found that binaural hearing abilities are impaired in many patients, and that the severity of the impairment changes over time after stroke onset. While many patients' lateralization abilities recovered toward later measurements, deteriorated performance was observed for others. Since stroke is such a common medical condition, its effect on binaural hearing should be investigated more thoroughly. The insights gained during this study can guide future research with respect to the management of confounding factors and to the relevance of choosing experimental conditions that best uncover impaired processing. Identifying which medical conditions lead to impaired binaural hearing might not only help in designing effective rehabilitation programs, but should also be communicated to the patients.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: zenodo.org, doi:10.5281/zenodo.8435686.

Ethics statement

The studies involving humans were approved by the Medical Research Ethics Board of the University of Oldenburg, Germany. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. PS: Conceptualization, Methodology, Supervision, Writing – review & editing. HP: Writing – review & editing. KW: Resources, Writing – review & editing. MD: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1322762/full#supplementary-material

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4 | Project III: Can an algorithm be used to steer experiments for more efficient measurements?

This chapter includes the research article "Auditory model-based parameter estimation and selection of the most informative experimental conditions", which was published by Acta Acustica in 2024 (https://doi.org/10.1051/aacus/2023064).

The goal of this study was to further develop and test the feasibility of a model-based experiment steering algorithm, that can be used to characterize individual impairments. Previously, the procedure proposed by Herrmann and Dietz (2021, Acta Acustica, 5:51) has only been tested in a computationally simulated patient. Here, the practical applicability of the steering procedure was tested with young normal-hearing listeners conducting a tone-in-noise detection experiment. On average, the same estimation accuracy was achieved in 42% of the time required by the standard adaptive method. Furthermore, improvements to an existing binaural model are presented. Since it is not a physiological model, no conclusions on the physiological causes of the individual's hearing impairment can be drawn. However, characterization of individual impairments in terms of functional parameters could be demonstrated.

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Contributions:
AD and MD contributed to the conception and design of the study. AD, MD, and AR planned the experimental procedures. AD, AR, JE, and MD further developed the model. AD and AR collected the data. AD performed the analysis. AD and MD interpreted the data. AD wrote the first draft of the manuscript. MD and JE revised the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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SCIENTIFIC ARTICLE OPEN ACCESS

Auditory model-based parameter estimation and selection of the most informative experimental conditions

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Abstract – Identifying the causes underlying a person's hearing impairment is challenging. It requires linking the results of listening tests to possible pathologies of the highly non-linear auditory system. This process is further aggravated by restrictions in measurement time, especially in clinical settings. A central but difficult goal is thus, to maximize the diagnostic information that is collectable within a given time frame. This study demonstrates the practical applicability of the model-based experiment-steering procedure introduced in Herrmann and Dietz (2021, Acta Acustica, 5:51). The approach chooses the stimuli that are presented and estimates the model parameters best predicting the subject's performance using a maximum-likelihood method. The same binaural tone-in-noise detection task was conducted using two measurement procedures: A standard adaptive staircase procedure and the model-based selection procedure based on an existing model. The model-steered procedure reached the same accuracy of model parameter estimation in on average only 42% of the time that was required with the standard adaptive procedure. Difficulties regarding the choice of a reliable model and reasonable discretization steps of its parameters are discussed. Although the physiological causes of an individual's results cannot directly be inferred using this procedure, a characterization in terms of functional parameters is possible.

Keywords: Binaural hearing, Tone-in-noise detection, Computational audiology, Model-based experiment steering, Audiological diagnostics

1 Introduction

The aim of audiological diagnostics is to identify the causes of a person's hearing impairment. A broad range of measurement techniques covering all kinds of deficits in the auditory system is available (for a review see [1]). To achieve a good diagnosis, comprehensive test batteries including subjective and objective tests are usually carried out as a first step. While some measurements specifically test for a particular pathology, combinations of tests are often required to differentiate between causes. This linking of data to the underlying cause or pathology is then the second step of the diagnostic process, posing challenges for audiologists, ENT doctors, and researchers alike, for three main reasons. First, a variety of pathologies and their combinations can cause a similar outcome. Second, the realization that more data on a particular experiment or stimulus would have been required often comes subsequent to the data collection. At this point, obtaining more data is sometimes no longer practically possible and often inconvenient. But even if data would exist in abundance, a third challenge remains: The auditory system consists of several highly non-linear stages intertwined with multiple efferent regulations. An experienced professional might be able to interpret the data and relate it to a unique pathology, but such diagnosis remains qualitative. A quantitative description of pathology-descriptive parameters with confidence ranges could provide information such as: The estimated loss of type I auditory fiber synapses range between 20% and 30%.

Computer models have been suggested as possible assistants in relating data to potential pathologies. Panda et al. [2] used a physiological model of the cochlea [3] to simulate data from a psychoacoustic test battery from hearing-impaired listeners. By varying one model parameter at a time, they created individualized computer models that enabled suggestions on underlying pathologies of their patients, although a combination of parameters would have yielded even better results in some cases. Model-based hearing diagnostics based on wideband tympanometry measurements was proposed by Sackmann et al. [4]. A finite element model of a human ear was used to simulate various pathologies like the stiffening of ligaments or joints to determine the most confident parameter set.

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Comprehensive physiological models of the auditory system require a large number of parameters to be confined (e.g., [4, 5]). In addition, physiological redundancies and co-dependencies in the system are useful to stabilize auditory perception against small disturbances or minor impairments, but they also lead to ambiguities in confining model parameters (e.g., [6]). Functional models, on the other hand, require fewer, though more abstract, parameters, such as filter bandwidth, internal noise, or attenuation. For instance, Plomp [7] presented a quantitative model pre- dicting speech understanding in noise that had only two parameters: attenuation and distortion. Confining these parameters does not lead to a description in terms of physiological characteristics. Nevertheless, such functional models can help with profiling hearing impaired persons and can predict the benefit to be expected from a hearing aid or hearing prosthesis. For instance, a prediction of common audiological functional parameters (CAFPAs) [8] from previously acquired audiological data using different machine learning algorithms has been presented in [9]. However, a large amount of data from different measurements is necessary.

The amount of experimental data required to confine the model parameters depends critically on two factors: Measurement accuracy (which depends on the square root of the number of trials) and the number of free model parameters (which causes a factorial effect on the number of parameter combinations). A single parameter can often be estimated from data obtained within a few minutes (e.g., [10]). Appraisal of three parameters, however, can already be expected to require several hours of data collection, at least in psychophysics (e.g. [11]). In many cases, it may be prudent to adjust the measurement, based on interim results. The approach of Sanchez Lopez et al. [12] for instance, can identify the most informative predictors in an auditory test battery, based on the preceding results. Instead of conducting all tests on each individual, only a subset of tests is sufficient for the characterization of listeners. These tests represent the nodes of a decision tree that lead to different diagnoses. Another way to confine the assessment of model parameters in a theoretically most time-efficient way is the maximum likelihood-based procedure running in parallel to the measurement and selecting those stimuli or tests that cause the best refinement in model parameters [11]. Theoretically, it can be used with any model and any portfolio of experiments. Nevertheless, the demands on the chosen model are high. It must provide good fits to all data without too many parameters. Otherwise, systematic deviations between model and data under any one experimental condition may cause the procedure to overemphasize this condition or to cause some other form of undesired behavior. Also, co-dependencies of the model parameters should be at a minimum.

The goal of the present study was to test the feasibility of model-based experiment steering for the prediction of model parameters. With this method, the experiment or the experimental conditions are varied such that prediction accuracy for diagnostically relevant model parameters is optimized. In contrast, standard adaptive methods choose experimental conditions that optimize prediction accuracy in the dimension of the adaptive stimulus parameter (e.g., tone level in dB). A characterization of the model-based experiment steering method in real instead of simulated subjects as shown by Herrmann and Dietz [11] was performed. As we are working particularly on binaural aspects, a simple model of binaural hearing was used for the present proof of concept. The chosen model by Encke and Dietz can be fit to accurately simulate individual tone-in-noise detection sensitivity for stimuli that differ in interaural phase and noise correlation [13].

2 Methods

2.1 Model-based selection framework

The basis of the model-based experiment steering that is applied for this proof-of-concept study was presented by Herrmann and Dietz in [11]. It is a likelihood-based adaptive procedure that operates in the model-parameter space and provides estimations for model parameters that can then be used for diagnosis. In order to get the most diagnostic information, the stimulus is adaptively varied such that the accuracy of the model parameter estimation is maximized. The framework can be separated into two parts: A likelihood-based parameter estimation module, and an experiment steering module.

The parameter estimation module estimates those model parameters with which the model and the participant produce the most similar data. This parameter estimation module can also be used on data that was collected conventionally, i.e., without model-based experiment steering. For the analysis, all experimental data are compared with pre-calculated model predictions (stored in the so-called model table), that are based on a selected set of parameter combinations. The dimensionality of the model table equals the sum of N model and M stimulus parameters.

The comparison of experimental data and the model table yields a multi-dimensional likelihood space with high values representing a high likelihood of the data being generated by a specific combination of model parameters. Different features of this likelihood space can be of interest, depending on the specific research question or clinical task. We decided to get estimates for the most likely model parameter value and the accuracy of the prediction for each model parameter in isolation. Therefore, the $N+M$-dimensional likelihood space is averaged over $N+M-1$ dimensions resulting in a compound likelihood distribution along the remaining parameter that was left out of the averaging. To derive the parameter estimation (mean, μ) and the accuracy of the estimation (standard deviation, σ) of this likelihood distribution we fit a Gaussian function to the distribution, with μ and σ as fit parameters. More precisely, for numerical convenience we fit a parabola function f of the form

$$f(x) = -\frac{(x-\mu)^2}{2\sigma^2} \tag{1}$$

to the log-likelihood values over the parameter values x. An offset parameter was not necessary, because the compound likelihood values were normalized by the maximal value, resulting a log-likelihood maximum of zero. The process is repeated N times, to fit the compound likelihood distribution of each of the N model parameters.

The second part of the framework is the model-based experiment steering (MoBES) module that runs in parallel to the data collection. It chooses the best experimental condition or the best stimulus to present to the subject next. With the MoBES module, the chosen stimulus is (based on the current model parameter estimates) expected to provide the most information for refining the model parameter estimates. The procedure chooses the stimulus condition that causes the largest reduction in σ. Within the framework, all model parameter values are discretized to simplify computation. Equation (1) can be applied to both continuous and discrete parameter values x. In the employed discrete version, x, μ, and σ can be expressed relative to the respective step size, i.e., in an arbitrary unit of "steps". For each parameter the discretization step size should be chosen so that it corresponds to a small but measurable and diagnostically relevant difference. This guideline should also ensure that all parameter steps influence the simulated results by a similar amount, but of course for different experimental conditions. The scale on which discretization is performed (e.g., linear, logarithmic, or other) must be chosen such that the likelihood values over x are approximately normally distributed.

2.2 Experiment and auditory model

We chose a tone-in-noise detection experiment in which a tone (either interaurally in phase: S_0 or anti-phasic: S_π) has to be detected in noise. The interaural correlation of the noise (ρ) can vary from -1 to 1, i.e., the noise is either anti-phasic ($N_{\rho=-1}$, referred to as N_π), interaurally fully correlated ($N_{\rho=1}$, referred to as N_0), or correlated to some extent in between these extreme conditions ($N_{-1<\rho<1}$). Detectability of the tone depends on its level and on the available interaural cues. The conditions without interaural cues (N_0S_0 and $N_\pi S_\pi$) are expected to be detected worst. Vice versa, detectability is expected to improve with increasing average interaural differences, being best for the conditions N_0S_0 and $N_\pi S_\pi$.

As noted in the Introduction, an accurate model is a crucial prerequisite for using the MoBES module. For this proof of concept, we opted for the analytic binaural processing model of Encke and Dietz [13]. It can predict correct rates of tone-in-noise detection for a variety of dichotic and diotic stimuli (such as the stimuli used in the experiment described above) with the three free parameters σ_{mon}, σ_{bin}, and $\hat{\rho}$. In the model the complex-valued correlation coefficient γ is calculated to quantify the amount of interaural phase difference (IPD) fluctuations, which is suggested to underlie binaural unmasking and is therefore used to estimate detectability. The model consists of a monaural and a binaural branch:

$$d' = \sqrt{d'^2_{\text{mon}} + d'^2_{\text{bin}}}. \tag{2}$$

The monaural branch is sensitive to differences in energy between the reference and the target signal:

$$d'_{\text{mon}} = \frac{\text{SNR}_{\text{eff}}}{\sigma_{\text{mon}}}. \tag{3}$$

The sensitivity is inversely proportional to model parameter σ_{mon}. The binaural branch is based on the difference between the Fisher's z-transformed complex correlation coefficients of a reference signal and a target signal:

$$d'_{\text{bin}} = \frac{|z[\hat{\rho}\gamma_r] - z[\hat{\rho}\gamma_t]|}{\sigma_{\text{bin}}}. \tag{4}$$

Since this transformation would result in infinite sensitivity to divergence of a fully coherent signal, which is not observed in the auditory system, the parameter $\hat{\rho}$ ($0 < \hat{\rho} < 1$) was introduced before z-transformation, thus limiting maximum sensitivity. As in the monaural branch, a model parameter σ_{bin} is used which is inversely proportional to binaural sensitivity, i.e., to the Euclidian distance between the z-transformed complex correlation coefficient of target and reference. The chosen experiment and model serve as one example use case of the MoBES procedure. Therefore, the model is only summarized here. Details can be found in [13].

Using this model as presented in [13], predicted detection thresholds are the same for detecting anti-phasic tones within diotic noise (N_0S_π) and for detecting in-phasic tones in anti-phasic noise ($N_\pi S_0$). This is not the case in behavioural data as shown for instance in [14]. We therefore modified the original model by introducing a fourth parameter into the model. It represents the decrease in $\hat{\rho}$ with increasing IPD, i.e., with increasing the argument of the complex correlation coefficient.

Introducing this additional parameter with a fading between the two most extreme correlation conditions of $+1$ (IPD $= 0$) and -1 (IPD $= \pi$) causes a slightly altered model architecture. The parameter that is limiting maximum sensitivity ($\hat{\rho}$ in Eq. (4)) is replaced by a term containing the parameter l_{max} limiting maximum sensitivity at IPD $= 0$ and the new parameter Δl_{max} that is representing the difference in sensitivity between the noise correlations of $+1$ and -1:

$$\hat{\rho} = 1 - 2^{l_{\text{max}} + \frac{(1-\rho)\Delta l_{\text{max}}}{2}}. \tag{5}$$

Since the complex correlation coefficient has no imaginary part in our experiment, the real part of the Pearson correlation coefficient ($\rho = \Re\{\gamma\}$) of the reference signal and of the target signal is used instead.

Model predictions are shown in Figure 1. In each panel, one model parameter was varied, while the other three parameters were set to a fixed value in the center of their respective range. As described above, each model parameter introduces changes to specific stimulus conditions, whereas others are not affected.

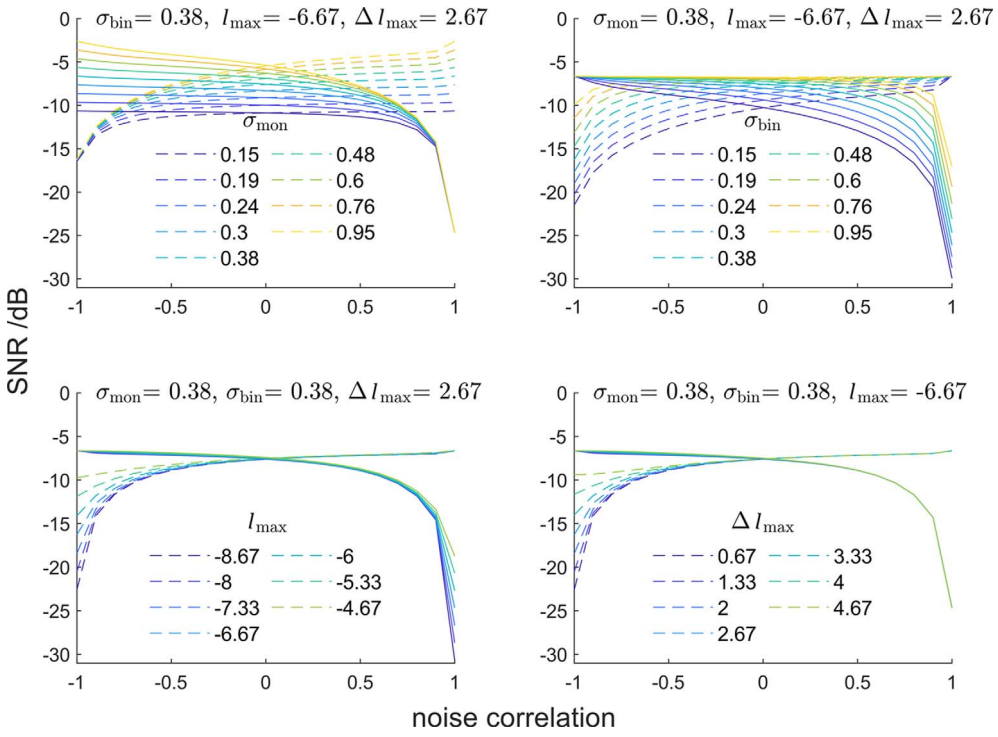

Figure 1. Model predictions (i.e., SNR corresponding to 79.4% correct) for different noise correlations (dashed lines: $N_\rho S_0$, solid lines: $N_\rho S_\pi$). In each panel, one model parameter was varied (color coding), while the other three parameters were set to a fixed value in the center of their respective range (shown at the top of each panel).

2.3 Measurements

Five young participants (age: 20–26 years; 3 female, 2 male) conducted the experiments with informed consent (approved by the ethics committee of the University of Oldenburg). The listeners received monetary compensation for the time spent on the experiments. Self-reported normal hearing was verified by clinical pure-tone audiometry (AT900, Auritec, Hamburg, Germany). None of the listeners had hearing thresholds exceeding 20 dB HL and there was no more than 10 dB difference in hearing threshold between the two ears at any octave frequency between 125 Hz and 10 kHz. The experiments were preceded by a training phase to familiarize the participants with the task. Two listeners had prior experience in binaural listening tasks (S1 and S5), the remaining three had no previous training in binaural hearing experiments.

2.3.1 Tasks and stimuli

The study consisted of two parts. All subjects participated in the same tone-in-noise detection task using (1) an adaptive staircase procedure and (2) the MoBES procedure. A four interval, two alternatives forced-choice experiment was conducted. Three intervals contained only the noise with a bandwidth of 100 Hz (Gaussian white noise with rectangular power-spectral density), arithmetically centered around 250 Hz. The second or third interval additionally contained a pure tone. This pure tone of 250 Hz was either interaurally in phase (S_0), or anti-phasic (S_π). The noise's interaural correlation ρ ranged from anti-correlated to fully correlated (-1, -0.75, -0.5, 0, 0.5, 0.75, 1). The stimuli were chosen to be comparable to those used in Robinson and Jeffress [15]. The duration of the stimulus intervals was 0.6 s, each separated by 0.2 s silence intervals. A cosine rise-and-fall window of 20 ms was applied to the noise and to the pure tone separately. The tone started when the noise was at full amplitude. The level of the noise was fixed at 67 dB SPL, whereas the tone level was varied adaptively during both experiments, as described below.

The listeners sat in a sound-attenuating booth on a comfortable chair in front of a computer screen and a computer keyboard. The signals were transmitted to an external audio interface (ADI-2 DAC FS, RME, Heimhausen, Germany) and presented using circumaural headphones (HD650, Sennheiser, Wedemark, Germany). Four rectangles lit up on the screen in succession during the four intervals in order to visually support the temporal sequence. The participants' task was to decide whether the second or the third interval differed from the first and last "cueing" intervals. Responses could only be given after the fourth interval and were entered by pressing the number "2" or "3" on the keyboard. The button press was followed by visual feedback on the screen indicating whether the choice was correct. After a delay of 250 ms, the next trial was presented.

2.3.2 Adaptive staircase procedure

The first portion of the experiments was a standard adaptive staircase procedure varying the tone level

following a 1-up 3-down rule converging to 79.4% correct responses [16]. The initial step size of 6 dB was halved to 3 dB after the second and again to 1.5 dB after the fourth reversal. The 1.5 dB step size was used for eight reversals. Complete runs under the 14 unique stimulus conditions (seven noise correlations, each with two different tone IPDs) were presented in random order, one complete run after the other. Each condition was repeated five times. Whenever feasible, a complete set comprising all these 14 conditions was measured on the same day. These five sets will be referred to as the five "measurement sets".

After completion of data collection, the likelihood-based parameter estimation module was applied to assess the most likely model parameters underlying these results. For visualization of the measured data, and for a comparison with the model predictions of the parameter estimation module, detection thresholds corresponding to 79.4% correct responses were computed from the average of the last eight reversals of the adaptive tracks.

2.3.3 Model-steered procedure

In the second part of the experiment, the measurement was conducted with the MoBES module introduced above. The range and discretization steps of the model parameters needed to be confined prior to the measurement phase.

Depending on how the parameters influenced the model outcome, the relation between the possible values was chosen differently. For σ_{mon} and σ_{bin}, factorial steps of $\sqrt[3]{2}$ ranging from 0.15 to 0.96 were chosen. Ranges from $-26/3$ to $-14/3$ for $l_{\max}$ and $2/3$ to $14/3$ for $\Delta l_{\max}$ were chosen with linear steps of $2/3$. The discretization was chosen for each parameter such that changes by one step led to approximately the same change in the SNR estimates. The effects of changes in each of the model parameters are shown in Figure 1. Changing σ_{mon} by one step always leads to changes in the estimated signal-to-noise ratio (SNR) of about 1 dB. Similar changes are observed for σ_{bin} but in other stimulus conditions. Increasing or decreasing parameters $l_{\max}$ and $\Delta l_{\max}$ by one step always leads to a change of about 2 dB but influences fewer stimulus conditions. Several piloting trials were necessary to ensure that the individual parameters of each subject were covered by the range of tested model parameters.

The model was run for all combinations of possible model parameters (model instances), and all combinations of possible stimulus parameters (stimulus conditions). The model table was pre-calculated overnight on a regular i5 laptop. The combination of the 2×7 stimulus conditions and the $9 \times 9 \times 7 \times 7$ model instances led to a total of 55,566 model calls for each of the 131 simulated stimulus levels to generate the psychometric functions. Instead of working with the original psychometrics functions (detection thresholds for different SNRs) for each stimulus, the amount of data in the model table is reduced by fitting a logistic function to the psychometric functions generated by the model for each combination of model instance and stimulus condition. The thresholds and slopes were obtained by a likelihood-based comparison of the psychometric functions generated by the model and logistic functions with a wide range of possible thresholds and slopes. The thresholds and slopes of the logistic functions with the best fit were saved in the model table. During the MoBES procedure and when using the parameter estimation module for pre-recorded data, only the model outcome stored in this model table (thresholds and slopes) was available for the likelihood-fitting.

With human subjects, unlike artificial subjects, switching between perceptually differing stimulus conditions across single trials leads to less reliable responses and poorer immediate performance (e.g., [17]). To circumvent this, two additions were made to the original procedure: First, the measurement phase was split into several measurement blocks, each with a fixed number of trials of the same stimulus condition (but varying level corresponding to the point of maximal expected information). For this study, 28 blocks, each containing 30 trials of the same condition, were completed by the subjects. After each block of 30 trials, the MoBES module computed the next stimulus condition to be presented. Second, the first two trials of each block were carried out merely to permit familiarity with the new stimulus condition but were neither saved nor used for the steering procedure. With this, a total of 840 trials (28 blocks $\times$ 30 trials) were presented, of which 784 trials (28 blocks $\times$ 28 trials) were stored.

The first four blocks were measured under predefined conditions before the likelihood-based measurement steering algorithm started. This was to initialize the model with a good starting point for the selection of the subsequent stimulus conditions. The conditions chosen for these initial blocks were: one purely diotic condition (N_0S_0), the two extreme dichotic conditions (N_0S_π and $N_\pi S_0$), plus one intermediate condition ($N_{\rho=0.75}S_\pi$). The choice of suitable initialization blocks also required knowledge acquired during the piloting of the study.

With the MoBES module, the accuracy of the model parameter estimation can be tracked and then used to terminate the experiments. With such a termination criterion, the measurement ends when the desired confidence range is reached for all model parameters. For the present "proof-of-concept" study, no termination criterion was set. Instead, a fixed number of 784 trials were conducted. This number was chosen to allow for comparisons between the two procedures, as the number of trials in one measurement set in the adaptive procedure was approximately 750 (depending on measurement set and subject).

3 Results

3.1 Adaptive staircase procedure

The tone-in-noise detection thresholds corresponding to 79.4% correct obtained with the five measurement sets of the adaptive staircase procedure are shown in Figure 2 where each panel shows data for one of the five subjects. Using the parameter estimation module, model parameters corresponding best to the subjects' data were obtained. The resulting model predictions for the $N_\rho S_0$ and $N_\rho S_\pi$ conditions are displayed as dashed and solid lines in

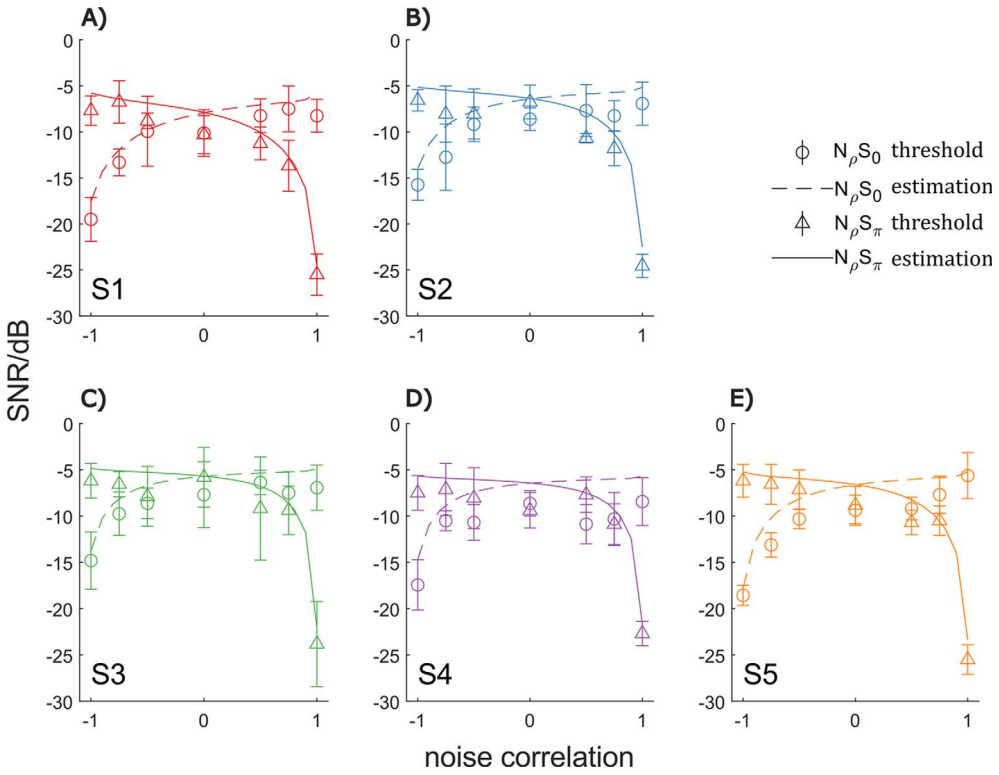

Figure 2. Tone-in-noise detection thresholds of the five subjects obtained with the adaptive staircase procedure. The triangles represent median thresholds for stimuli with anti-phasic tones ($N_\rho S_\pi$), the circles for tones that were inter-aurally in phase ($N_\rho S_0$). The inter-quartile range of the five trials of each condition is represented as error bars. The dashed lines (anti-phasic tones, $N_\rho S_\pi$) and solid lines (in-phasic tones, $N_\rho S_0$) represent the SNR thresholds predicted by the model with the parameters estimated by the parameter estimation module.

the same figure and show the modelled SNR for 79.4% correct.

As expected, the thresholds for the conditions without binaural cues (N_0S_0, the right-most circle and $N_\pi S_\pi$, the left-most triangle) are the highest. Thresholds improved with increasing average IPD difference between masker and target, until the lowest thresholds were obtained for $N_\pi S_0$ (leftmost circle) and $N_0 S_\pi$ (rightmost triangle). Within the latter condition, all subjects reached the lowest of their thresholds.

The model predictions of the parameter estimation module captures the behavior of all subjects, with only small deviations for single stimulus conditions (see Fig. 2). The performance is slightly underestimated by the model predicitons in the conditions with the worst behavioral thresholds. The coefficient of determination R^2 ranged between 0.64 for subject S4 and 0.85 for subject S5 and was averaged 0.80. The SNR thresholds obtained with the adaptive procedure for the conditions N_0S_0 and N_0S_π are shown in Figures 3A and 3D. Estimates for the four model parameters based on the five measurement sets individually ("1", "2", "3", "4", "5", and the median of these results: "μ") and all data analyzed together ("all") are shown in Figures 3B, 3C, 3E, and 3F. It becomes obvious that the detection thresholds and model parameter estimates differ between the five measurement sets. The SNR of the N_0S_0 condition drops over time, which is reflected in model parameter σ_{mon} and to some extent also in σ_{bin}. The variability in the model parameters $l_{\max}$ and $\Delta l_{\max}$ seems not to follow any systematic trend. The SNR estimated from all five measurement sets together differs for many conditions from the median SNR of the five adaptive measurement sets analyzed individually. This can be seen for instance in Figure 3A when comparing the circles to the dots. The difference ranges up to 5 standard deviations of the adaptive measurement sets. The above-mentioned difference is not reflected in the model parameters estimated from the five measurement sets together (circles) and the median of the five individual measurement sets (dots). For the model parameters the maximal difference is 0.6 standard deviations.

3.2 Model-steered procedure

When using the MoBES module, model parameters were estimated for every trial based on the compound likelihood for each model parameter. Figure 4 shows the development of the compound likelihood (mean over the other three parameters and all stimulus parameters after setting the maximum of each trial to zero) for each of the four parameters over trials for subject S4 in the upper four panels. Over the course of the trials, the likelihood

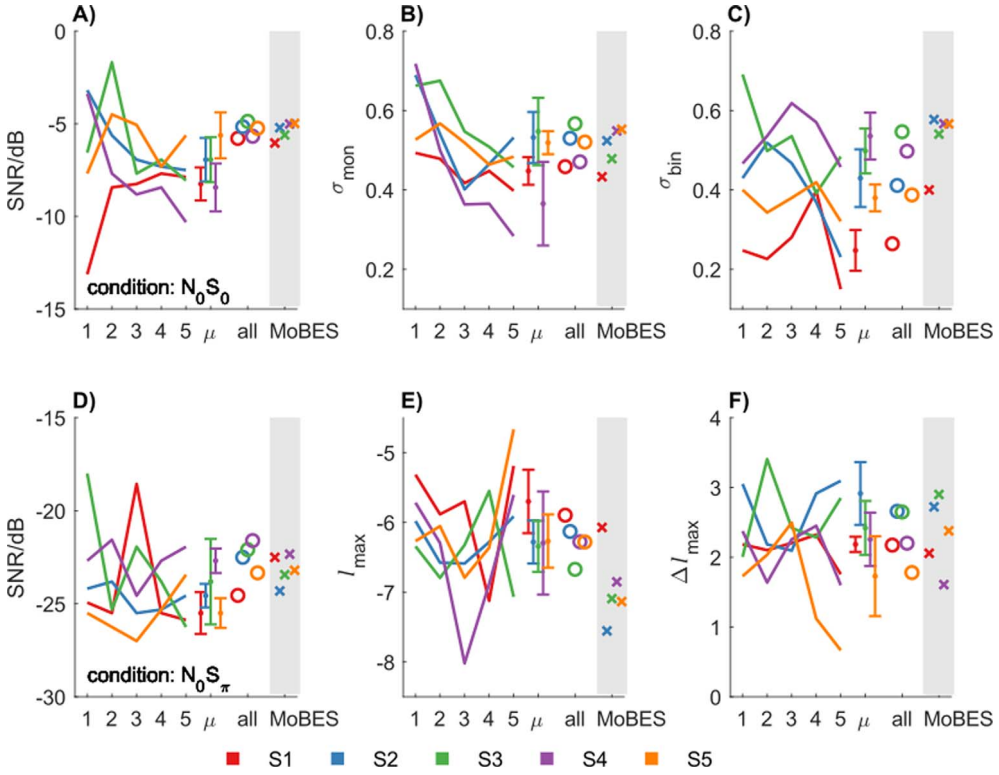

Figure 3. Detection thresholds (SNR, panels A, D) obtained with the adaptive procedure and model parameter estimates (panels B, C, E, F) determined with the parameter estimation module for the adaptive experiment. The lines represent the data for the five individual measurement sets. Their medians and inter-quartile ranges are shown with the dot and the error bars. The circles show the model parameter estimates for running the estimation module for the data of all five sets together. The model parameters for the data obtained with the MoBES procedure are indicated by the crosses above the gray shading.

distribution reduced in width. The bottom panel shows the stimuli chosen by the procedure.

Lower values of σ_{mon} correspond to lower thresholds in the diotic (or monaural) conditions. Lower values of σ_{bin} correspond to lower thresholds in those conditions with interaural differences. As described in the Methods section, the parameter l_{max} mainly affects the thresholds for $N_\pi S_0$ and $N_0 S_\pi$, whereas Δl_{max} influences the difference between $N_\pi S_0$ and $N_0 S_\pi$. This can be observed in Figure 4: The first stimulus condition in the experiment ($N_0 S_\pi$) did not deliver information on the monaural threshold. For this reason, the estimation of σ_{mon} only starts refining with the second block ($N_0 S_0$). Similarly, parameter Δl_{max} (the difference between $N_0 S_\pi$ and $N_\pi S_0$) can only be estimated starting with the first trials of $N_\pi S_0$ in block number three. After the four initialization blocks were presented, starting with trial number 113 (at the dashed black line), the experiment steering module selected different stimulus conditions, emphasizing $N_0 S_\pi$, $N_{\rho=0.75} S_\pi$, and, to a lesser degree, $N_\pi S_0$, and $N_\pi S_\pi$. Noise correlation values between those were only rarely chosen (once in S1 and S4, twice in S2, and never in S3 and S5). Comparable patterns and similar model parameter estimates were also found for the other subjects (see Supplementary Figures 1–4). The estimates for the four model parameters based on data from the MoBES procedure are shown in the grey shading of Figures 3B–3F and in Figure 5.

The mean of the confidence ranges (variance of the parabola fit, σ in Eq. (1)), which can be qualitatively estimated for subject S4 from the width of the likelihood surfaces for the four parameters in Figure 4, is shown for all subjects in Figure 6. As a global trend, the confidence ranges decreased with the number of trials. For instance, the mean confidence range over the four parameters for subject S4 decreased from 2.14 steps at the start of the model-steering to 0.36 steps after the last trial. Comparable decreases were also found for the other subjects. After the final trial, the procedure reached a mean accuracy between 0.32 steps and 0.36 steps for the different subjects (mean: 0.35 steps).

3.3 Comparison of the two procedures

The detection thresholds (SNR) and the model parameter estimates with the data acquired using the adaptive and the MoBES procedure are shown in Figure 3 (panels A, D and panels B, C, E, F, respectively). The SNR thresholds calculated from all five measurement sets of the adaptive procedure (circles) and those obtained by the MoBES procedure (crosses) are very similar. The differences in

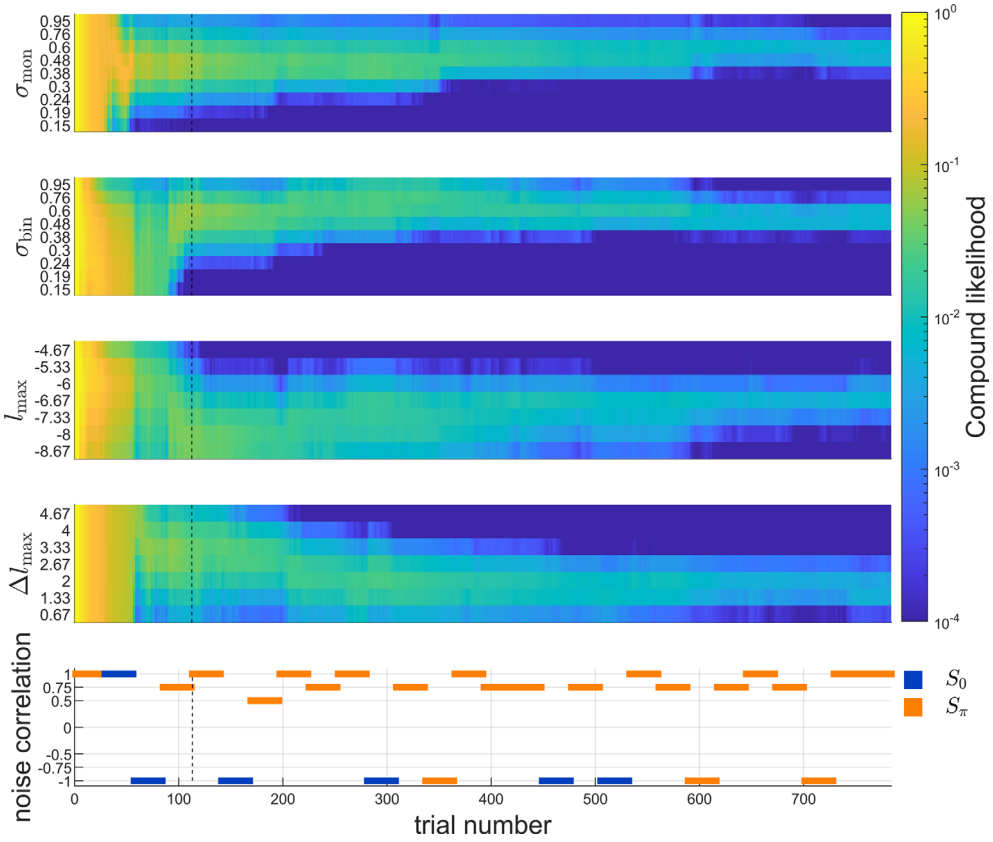

Figure 4. Compound likelihood (mean over the other three parameters and all stimulus parameters after setting the maximum of each trial to zero) for each of the four model parameters in the upper four panels for subject S4. The stimuli chosen by the procedure across trials are shown in the bottom panel. The dashed black line indicates the end of the initialization blocks and the start of the model steering with trial number 113.

SNR ranged between 0 and 2.0 times the standard deviation of the five adaptive measurement sets in all subjects and conditions with two exceptions: The estimates differed in subject S5 for the condition $N_\pi S_0$ by 3.0 and for subject S2 for the condition $N_0 S_\pi$ by 2.5 standard deviations.

As shown in Figure 3, the difference between the model parameters estimated from data obtained with the adaptive procedure (circles) and the MoBES procedures (crosses) ranges in all but two cases between 0.1 and 1.6 times the standard deviation of the parameters across the five adaptive measurement sets. Only in subject S2 (blue) the estimates from the two procedures differ by 4.5 standard deviations for parameter l_{max} and in subject S5 (orange) by 4.4 standard deviations for parameter σ_{bin}. For a better comparability and to detect possible biases of the two procedures, estimations of the four model parameters for the two procedures are shown in Figure 5. It becomes evident that the difference between the estimations by the two procedures depends on the specific model parameter and subject. However, a bias towards lower estimations for one procedure might be present for the parameters σ_{bin} and l_{max}. In general, parameter estimations by the two procedures are comparable and the model parameter estimations do not differ substantially between the subjects.

Figure 6 shows the mean confidence ranges across the four model parameters as a function of trials for the adaptive procedure and the MoBES procedure. With the latter, only 874 trials were recorded. For the adaptive procedure, confidence ranges are only shown after each full measurement set of 14 conditions (651–786 trials). These measurement sets differed slightly in the number of trials as the number of trials needed for eight reversals at the final step size differed between the subjects and measurement sets. In general, a decrease of confidence ranges over trials was observed, with a steeper decrease in the model-steered data. For instance, for subject S1, the mean confidence range after the first measurement set of the adaptive procedure (693 trials) was 0.82 steps. Using the MoBES module the same or a smaller value was reached after 302 trials. The same confidence range was achieved more than twice as fast with the MoBES module. To reach the same confidence range using the adaptive procedure, 1.9–3.7 times more trials were necessary than with the model-steering procedure.

4 Discussion

This study sought to test the feasibility of model-based experiment steering in human subjects, after a preceding study by Herrmann and Dietz [11] had concluded that there would be a theoretical advantage of the proposed procedure

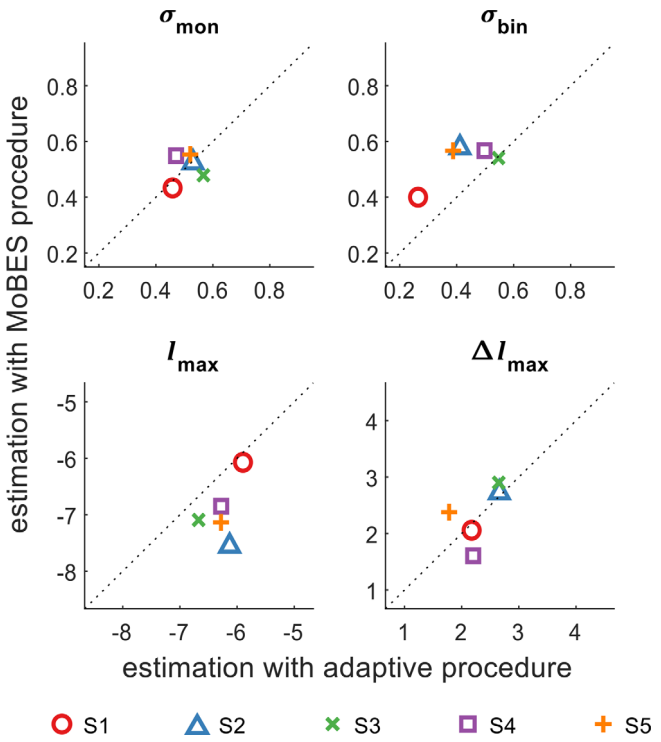

Figure 5. Estimations for the four model parameters based on all data from the standard adaptive procedure and the MoBES procedure for subjects S1 to S5. The dashed line indicates equal estimations based on the two procedures. Color and marker shape vary for the individual subjects.

over sequential measure-and-fit approaches. In the current study, the model-steered procedure was tested on young normal-hearing subjects, while the previous study only tested an artificial "in-silico patient". This attempt was successful for two reasons. First, the estimated model parameters were sufficiently close to those obtained from the results of the standard adaptive procedure. Second, the same accuracy in model parameter estimates was obtained in 27–60% of the time required by the standard adaptive method. The proposed measurement procedure can assist in linking data to the underlying pathology, or to a parametric description of the individuals' hearing abilities. The procedure will steer towards those measurements that can disentangle different causes of the observed behavior, even in the complex auditory processing chain. As a prerequisite for this becoming reality in clinical settings, models with high diagnostic resolution need to be developed. In the current study, an existing simple model of binaural processing was used, but slightly adapted as a first attempt to characterize a subject in the most time-efficient way. Even though the diagnostic value of the model parameters is not clear in this study, it served as proof of concept.

The duration of measurements is limited in clinical settings. However, keeping measurement times as short as possible is also of importance for another reason: With longer measurement times, unaccounted factors could influence the data. Fatigue, attention, motivation or effects specific to single measurement days may potentially confound the parameter evaluations. Using the model-steering procedure, mean confidence ranges of 0.35 steps were reached for the four model parameters after less than 1.5 h. To put it another way, the model-steered procedure reached the same accuracy of model parameter estimation on average in 42% of the time required by the standard adaptive procedure. Attempts to shorten measurement times in clinical settings have been presented before (e.g., fast audiometric testing presented in [18]). In contrast to previous studies, the present study aimed for a procedure to reduce measurement times that is not restricted to a specific experiment.

One of the main concerns remains the choice of an accurate model with diagnostic value. The approach with an auditory processing model requires the faithful simulation of the whole chain from stimulus presentation, through internal processing, to the subject's response, or to other measured data. We were able to perform a proof-of-concept but could only characterize those aspects that are relevant for tone-in-noise detection sensitivity at one frequency and only for normal-hearing subjects. The four model parameters cannot be directly related to hearing difficulties. The parameters σ_{mon} and σ_{bin} describe general monaural and binaural abilities of the participant. Importantly, these two parameters are both influenced by disturbances at various levels of the auditory system. Disturbances can range from conductive hearing loss and hair cell loss to cognitive factors such as attentional deficits. Parameter l_{max} is related to the best performance achieved by binaural hearing. Therefore, it is not fully independent of σ_{bin}. The physiological basis of Δl_{max} (difference in the firing rates to the conditions $N_\pi S_0$ and $N_0 S_\pi$) is described in [19] but can also not be based on one process alone. This overlap in causes and effects is common in functional models. However, to diagnose the causes of hearing difficulties, other models are needed.

In order to use the approach with hearing impaired subjects, additional model parameters must be allowed to vary. For example, the parameter "effective bandwidth of the auditory periphery" is fixed in our model. Therefore, it cannot serve as a realistic model for patients with outer hair cell damage. Of course, this bandwidth could be an additional parameter to fit, as already demonstrated in [11], and most other specific extensions are also expected to be compatible with the approach. The problem is the number of parameters, especially as many of the parameters may differ from frequency to frequency. At the same time other parameters, such as the endocochlear potential are inherently frequency-independent, but influence hearing differently across frequency [2], further complicating a comprehensive parameterization. Abstract models that even avoid a simulation of auditory processing may be more realistic candidates for model-steered profiling. Abstract models can be employed if, instead of a detailed diagnosis, the focus of interest is rather on the consequences of altered auditory processing in real-world listening scenarios. Ideally, each model parameter should directly relate to a practical outcome, e.g., it can be a hearing-aid fitting parameter (similar to the model used by Plomp [7]).

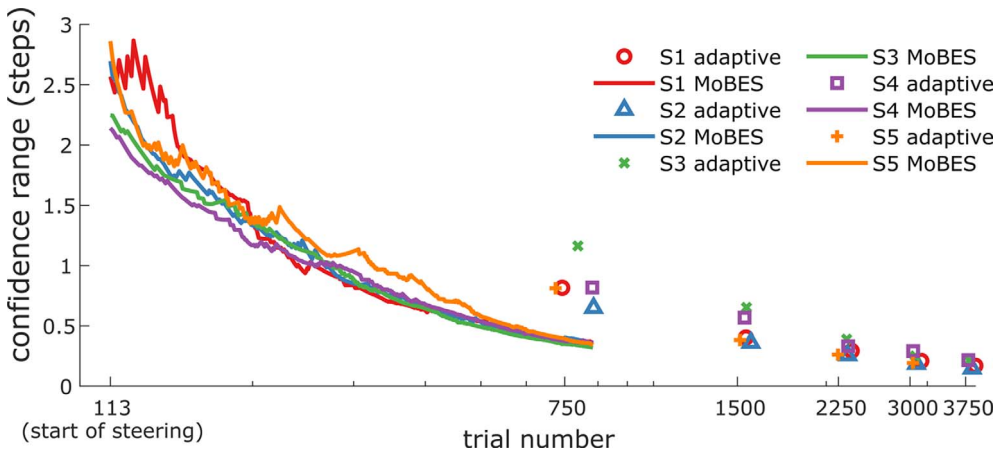

Figure 6. Mean of confidence ranges (in steps) averaged across the four model parameters over trials for subjects S1 to S5. The estimates for the model-steered procedure are depicted with lines, for the adaptive procedure with symbols. Color and marker shape vary for the individual subjects.

Having decided on a particular model, choosing meaningful ranges and discretization for the model parameters remains a critical point. In the best case, each step leads to similarly large changes in model predictions as shown in Figure 1. Matching the effect size of parameter steps is also important in the light of co-dependencies between model parameters. Preferably, changes by one discrete step in one parameter should not force another co-dependent parameter to change by more than one step. It is also important that estimated parameters do not reach the boundary of the parameter range of the previously stored model table. To fit the data best, the apex of the parabola that is used to obtain parameter estimation and confidence range, would possibly be outside the boundaries. The steepness would be very small, resulting in confidence ranges spanning the entire possible range of parameters. Such corrupted confidence ranges lead to the choice of non-optimal next stimulus conditions. An additional advantage of matching the effect size of parameter steps is that it allows the steering procedure to minimize the unweighted sum of confidence ranges, as measured in numbers of steps. The procedure is then expected to provide similar accuracy for all parameters without being biased towards minimizing the confidence ranges of some model parameters more than others. Extensive piloting with adjustments to the ranges and step sizes of the parameters preceded data collection. The need for such time-consuming preparation makes the method feasible only when the subsequent measurements benefit substantially from it. This is the case, for example, when many participants are to be measured (i.e., the extensive piloting time is outweighed by considerable savings in measurement time) or when the measurement time with these participants is restricted very much (i.e., the method allows for a better use of the limited time). Both are often the case in clinically-oriented patient studies.

Independent of the exact experiment or the population that is measured, at least two sources of variability can influence the data in behavioral measurements. First, the variability of responses over time, which can be influenced by training, fatigue, attention, motivation, and other factors. Second, the pathology-induced changes to the system that we aim to quantify in terms of model parameter estimates. A training effect was observed for the standard adaptive measurements. The SNR thresholds were significantly lower in the fifth measurement set compared to the first measurement set in all but one participant. This training effect can be seen for some participants in the two conditions shown in Figures 3A and 3D and might be present within the results of the model-steered experiment, too. Importantly, the MoBES procedure does not operate in the dimension of threshold values as those procedures reviewed in Leek [20], but in the dimension of model parameters, trying to minimize the confidence ranges of the model parameter estimates. In Figure 3 it can be seen that the inter-individual differences in parameter estimates were smaller than the variability from measurement set to measurement set in the adaptive experiment. Parameter estimations of the two procedures and the different subjects are comparable (see Fig. 5). This is expected, because all the subjects were young, normal-hearing participants and should therefore not differ substantially in their thresholds. Future studies with hearing-impaired subjects are expected to reveal the full potential of the MoBES procedure by providing individual differences in the model parameter estimations.

Besides the focus of more efficient diagnostic measurements, one key advantage of using the MoBES procedure is the way it provides the researcher with a deeper understanding of the model in use. When comparing the selected stimulus conditions (see the bottom panel in Fig. 4) to the changes in the model prediction in Figure 1, it becomes obvious which stimulus conditions provide the most information about each of the model parameters. $N_\pi S_\pi$ is chosen, as it only depends on σ_{mon}. The frequently chosen condition

$N_{\rho=\ 0.75}S_{\pi}$, for example, mainly informs about $\sigma_{\text{bin.}}$ However, the more complex the models are, the more difficult it is to comprehend these relationships. Even when not using the MoBES module to steer the measurement, using it in the piloting phase of an experiment might add valuable knowledge about the inner mechanics of the model or which conditions should be measured in the main part of the experiment.

To finish, we note that the model-based steering procedure presented in this study is a useful tool for future research on auditory diagnostics. Characterization of individuals in terms of abstract parameters that influence hearing-aid fitting or maybe the choice of a hearing support device type is possible – at least in theory. Scientifically, both the likelihood-based fitting and the model-based steering foster a deeper understanding of the models in use. The procedure also offers insights into its interaction with fitting tools, measurement procedures, and subject peculiarities that are not captured by the model. Specifically, as argued by Herrmann and Dietz [11], tracing why the model chooses certain stimuli and in which order, is highly informative, even for an improvement of conventional manual measurement selection. It also facilitates a deeper understanding of the impact of each model parameter in general, and of each parameter's discretization steps. The procedure thus provides new perspectives for the design of diagnostic models and experiments.

5 Conclusion

The aim of this study was to test the feasibility of model-based experiment steering for the prediction of model parameters on the example of a tone-in-noise detection experiment. We showed that the procedure can be used to estimate model parameters more time-efficiently than a standard adaptive method. Thus, in the future, it can be used to assist in linking data to the underlying pathology, or to a parametric description of the individuals' abilities. The distant goal of diagnosing the causes of a person's hearing impairment has not yet been achieved because auditory models have either too many parameters or miss out on some diagnostically relevant aspects. However, the procedure already enables a deeper understanding of the model used and the impact of each model parameter. This is particularly important when working with more complex models. Furthermore, the procedure is not limited to audiological diagnostics, but can also be used in various fields other than audiology.

Conflict of interest

The authors declared no conflicts of interests.

Data availability statement

The Matlab code and data analyzed in this study are available online [21].

Supplementary figures

Supplementary figures are available at https://acta-acustica.edpsciences.org/10.1051/aacus/2023064/olm.

Figure S1: Compound likelihood (mean over the other three parameters and all stimulus parameters after setting the maximum of each trial to zero) for each of the four model parameters in the upper four panels for subject S1. The stimuli chosen by the procedure across trials are shown in the bottom panel. The dashed black line indicates the end of the initialization blocks and the start of the model steering with trial number 113.

Figure S2: Compound likelihood (mean over the other three parameters and all stimulus parameters after setting the maximum of each trial to zero) for each of the four model parameters in the upper four panels for subject S2. The stimuli chosen by the procedure across trials are shown in the bottom panel. The dashed black line indicates the end of the initialization blocks and the start of the model steering with trial number 113.

Figure S3: Compound likelihood (mean over the other three parameters and all stimulus parameters after setting the maximum of each trial to zero) for each of the four model parameters in the upper four panels for subject S3. The stimuli chosen by the procedure across trials are shown in the bottom panel. The dashed black line indicates the end of the initialization blocks and the start of the model steering with trial number 113.

Figure S4: Compound likelihood (mean over the other three parameters and all stimulus parameters after setting the maximum of each trial to zero) for each of the four model parameters in the upper four panels for subject S5. The stimuli chosen by the procedure across trials are shown in the bottom panel. The dashed black line indicates the end of the initialization blocks and the start of the model steering with trial number 113.

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5 | General Discussion

Chapter 1 introduced the topics relevant to understanding the questions covered in the subsequent research articles. The main part of the thesis (Chapters 2-4) was devoted to these articles. The last chapter aims to tie up any loose ends and to discuss them on a more general level. The chapter begins with a summary of the key findings of each project (Section 5.1). Then, the implications that emerge from the three projects are discussed in Section 5.2 and methodological considerations are addressed in Section 5.3. All three projects raised the relevance of individualized diagnostics and its potential for future developments, as shown in Section 5.4. The thesis ends with a concluding statement in Section 5.5.

5.1 Main Findings of Each Project

5.1.1 Project I

The first project aimed to explore the individual binaural perception of stroke patients in the acute phase of stroke. A tone-in-noise detection task and a lateralization task were conducted in 50 acute-phase stroke patients with various lesion locations encompassing all central binaural processing stages. This has not been done in any previous study. Binaural impairments have been found in the majority of patients. More specifically, the following observations were made:

- Non-convergent tracks in the tone-in-noise detection task (i.e., not allowing for the calculation of the BMLD) were produced by six patients with lesions of basal ganglia or multiple lesioned areas. Three of the remaining 44 patients showed a reduced BMLD.
- As expected with lesions of the first stages of binaural interaction, patients with a brainstem lesion showed distortions in binaural perception, such as categorical lateralization of ILD and ITD stimuli.
- In all cases with lesions of the left thalamus, a shift of the lateralization pattern was observed. However, across all patients, the magnitude of asymmetry in hearing thresholds correlated with possible lateralization shifts.
- In patients with basal ganglia lesions, a high trial-to-trial variability was observed, which may be attributed to attention deficits.

- A strong difference between left- and right-hemispheric lesions was found in patients with basal ganglia lesions. Lesions in the right hemisphere led to stronger lateralization impairments than left-hemispheric lesions.
- Patients with multiple lesions in one or both hemispheres showed increased variability and a decreased slope of lateralization.
- Impaired contralesional lateralization was found in patients with lesions of the brainstem and right cortical areas, consistent with previous literature.
- In general, effects on the lateralization patterns were mainly found in the contralesional hemifield, but for some patients also in the ipsilesional hemifield.

The performance in the lateralization task (explicit use of binaural information) differed individually and on a group level from the control subjects. In contrast, the performance in the tone-in-noise detection task (implicit use of binaural information) was only impaired in a few cases. In general, a high number of stroke patients, even with only mild symptoms of stroke, showed severe deficits in binaural hearing tasks in the acute phase of stroke. The occurrence of a multitude of impairments in the acute phase results indicates that the assumption was correct that plasticity, compensatory mechanisms or relearning are not to be expected shortly after stroke. Thus, the findings provided insights into the involvement of damaged structures in binaural processing in individual patients.

5.1.2 Project II

The aim of Project II was to determine how binaural perception changes across the phases of stroke recovery. Binaural hearing after stroke has never before been evaluated in a longitudinal study. Patients who were part of Project I were re-invited to this study in the subacute and chronic phases of stroke, and 31 patients of the original group did the tone-in-noise detection task and the lateralization task again. In comparison to the many lesion group-specific and individual impairments observed in the acute phase of stroke, the recovery of binaural hearing appears to be even more individual. A selection of observations is listed below:

- At the group level, the performance in both binaural tasks (lateralization and tone-in-noise detection) remained constant over time.
- The BMLD was not measurable in two of 31 patients in the acute phase, but both had a BMLD within the normal range in their last measurement. Two patients had a reduced BMLD in the acute phase. One of them recovered to normal values in the later phases.

- Highly individual behavior was observed across the phases of stroke recovery for the lateralization task: Some patients' performance improved, whereas others' deteriorated. The recovery process was not consistent within lesion-location groups.
- While strong changes in the individual lateralization patterns were observed across the acute and subacute phases, the pattern changed little from the subacute to the chronic phase.
- Despite mild or absent clinical stroke symptoms in the acute phase, six of 22 patients still showed substantially impaired lateralization patterns in the chronic phase.
- Several confounding factors, such as age, hearing loss, and general well-being may have individually affected the recovery process.

The performance in the tone-in-noise detection task mainly recovered in the few patients who showed difficulties in the acute phase. The performance remained on a good level in the rest of the patients. Using binaural information for the lateralization task recovered in some patients, whereas in others no recovery or even deterioration in lateralization was observed until the last measurement. The strongest changes in lateralization patterns were observed up to the subacute phase. These changes in lateralization patterns were not consistent for patients with similar lesion locations, suggesting a highly individual recovery process. Overall, for many, but not all patients, the hypothesis that binaural perception recovers towards later measurements was confirmed. However, the limited time available with the patients prevented a more thorough examination of the individual factors that foster recovery or deterioration.

5.1.3 Project III

The third project aimed to further develop and test the applicability of a model-based experiment steering (MoBES) procedure for the time-efficient characterization of individual impairments. A tone-in-noise detection experiment was conducted with young normal-hearing participants using both the MoBES procedure and a standard adaptive measurement procedure. Since the steering algorithm is based on a computational model of the system under investigation, the project also required the further development of an existing binaural model. The main findings of this project are the following:

- An analytic binaural processing model based on the complex correlation coefficient of the stimulus was used. Originally, it contained three parameters.

Adding a fourth parameter to this model allowed us to predict the difference in detectability of the conditions N_0S_π and $N_\pi S_0$.

- The model parameters that were estimated using the MoBES procedure and the standard adaptive procedure did not differ substantially.
- Equal accuracy in parameter estimation was reached on average in 42% of the time required by the standard adaptive procedure.
- To perform audiological diagnostics with hearing-impaired participants in the future, a model with diagnostically relevant parameters needs to be developed.
- The MoBES procedure provided a deeper understanding of the model being used and the impact of each model parameter, which can be particularly important when working with more complex models.
- Knowing which conditions are frequently chosen in the piloting phase of experiments could help to design experimental procedures more efficiently, even if the MoBES procedure is not used for the main experiment.

We showed that the MoBES procedure can be used for more time-efficient measurements already. In addition, the procedure provides insight into the model used and the information content of specific measurement conditions. To use it for diagnostics, the critical factor is the choice of a model with diagnostically relevant parameters. To date, there is no such comprehensive binaural auditory model that can simulate all kinds of binaural hearing tasks, but the study presented the further development of an existing model. Overall, the study confirmed that the MoBES procedure can be used in the future for time-efficient diagnostics, i.e., linking data to a parametric description of the individual's pathology.

5.2 Key Implications Across Projects

The same population of stroke patients was studied in Projects I and II. Impairments in binaural auditory performance were observed in the acute, subacute, and chronic phases of stroke, although the clinically registered symptoms of stroke were mild. The divergences from the lateralization performance of the control group were partly consistent in stroke patients with similar lesion locations, but individual impairments were also found. In contrast, the recovery of lateralization abilities did not depend on the lesion site but was highly individual. Even though lateralization impairments were present in the majority of patients, only a few had difficulties in the tone-in-noise detection task. In other words, many patients showed distortions when using binaural information explicitly, while they were able to correctly use binaural information for

the implicit task. The initial hypothesis was that altered encoding (caused by lesions at the brainstem level) would lead to difficulties in both tasks, but this was only the case in one patient. Instead, it appears that the auditory system adapts individually to make the best use of the available information. The answer to how the healthy brain encodes and decodes spatial position can only be partially determined from our data. On the other hand, findings on individual impairments are of fundamental clinical interest and can be relevant for stroke rehabilitation. Particularly in the interdisciplinary field of hearing research, clinical applicability compensates for the limited direct benefit of the results for basic research.

Plasticity, compensatory mechanisms, and relearning may mainly affect everyday listening scenarios like the localization of sound sources and the segregation of auditory streams. Keuroghlian and Knudsen (2007) showed that recovery was only found for those acoustic features that were trained. Therefore, the intracranial perception of the rather unnatural stimuli in the lateralization task may not have recovered in some patients because such stimuli are not experienced outside the laboratory. Another possibility is that a distorted representation of the isolated binaural cues may be functional. It may accommodate a correct representation of spatial location (supported by a combination of binaural and monaural cues as well as non-auditory information) despite altered inputs. Regardless of their cause, one likely consequence of perceptual distortions is that additional capacities need to be allocated to binaural listening tasks. This, in turn, could lead to higher listening effort in binaural hearing situations, possibly interfering with other tasks such as the processing and memorizing of what another person has said (Peelle, 2017).

From a more methodological point of view, Projects I and II highlighted the need for efficient individualized measurements, which was addressed in Project III. The study confirmed that the MoBES procedure is feasible for time-efficient measurements. The applicability was demonstrated with a binaural hearing experiment, but the procedure can be used for any kind of experiment in various fields, not only in auditory research. The most important missing element identified in Project III is a model of the auditory system with few, but diagnostically relevant parameters. To date, there is no comprehensive model of the binaural system (i.e., a model spanning all processing stages) that can faithfully simulate the individual nature of pathological binaural hearing with only few parameters. However, Matlab scripts and measurement data of all three projects are accessible to anyone interested (links to the repositories can be found in Chapters 2-4) and may be used to generate and validate model ideas.

5.3 Methodological Considerations

As summarized by Gallun (2021), measurements in clinical settings entail challenges that are not encountered in experiments conducted in well-controlled laboratories with participants assigned to a particular group. Such challenges were also experienced in Projects I and II: The main effects of stroke on binaural perception were accompanied by factors like hearing loss, cognitive decline, possible old damage to brain tissue, motivational deficits, and many others. These influences should be equally present in the stroke cohort and the age-matched control group and some of them were included as covariates for statistical analyses. Nevertheless, it is possible that the combination of stroke and any of these factors influenced binaural perception more than each single factor. Although the total number of patients was rather high in comparison to related single-appointment studies (e.g., 21 in Bamiou et al. (2012); 22 in Aharonson et al. (1998); 50 in Spierer et al. (2009)), some lesion groups consisted of only a few patients, which impeded statistical analyses. On top of that, since the main focus of the thesis was on individual findings more than on group effects, the results are undoubtedly influenced by individual confounding factors and must be interpreted with caution. Another constraint is that, unlike ablation studies in the animal model, natural stroke lesions do not result in a complete loss of a specific brain area, which complicates the interpretation of the results. Because the magnetic resonance images were obtained as part of the clinical routine using 1.5 Tesla scanners, their resolution did not allow for detailed estimation of lesion locations at the scale of individual small nuclei such as the MSO or LSO. In addition, external factors, such as a noisy environment or the limited time available for the behavioral experiments influenced the measurement results. For example, training runs were not possible but may have been necessary for stroke patients in acute distress. In summary, more time would have been needed to further characterize individual impairments and all influencing factors.

The MoBES procedure presented in Project III addresses some of the methodological shortcomings mentioned above by allowing individual characterization of patients based on predefined diagnostic parameters. In addition to the task-dependent internal parameters, the models on which the steering procedure is based could theoretically also include task-independent internal factors as parameters. However, there is still a major obstacle to overcome in order to move this method from basic research to more applied clinical research in the future: So far, the MoBES method has not been used to control experiments with hearing-impaired subjects or patients with other types of impairments. This is because a solid understanding of the underlying processes in the form of a model with few impairment-related parameters is required. For instance,

the model used for the proof-of-concept in Project III cannot account for stroke-related processing deficits or hearing loss in its current version, nor can it be used to simulate the performance in a lateralization task.

5.4 Future Directions

Due to the importance of binaural hearing for communication, the individual effects of stroke, as described in Projects I and II, should be investigated in the future, even in patients with clinically mild stroke symptoms. Knowing which specific listening scenarios pose challenges is important for persons affected, as impaired hearing has been shown to negatively affect quality of life measures (reviewed by Tseng et al., 2018). Only through identifying specific deficiencies can targeted training as proposed by Wright and Zhang (2006) be customized for each patient. This targeted training will presumably be most effective when provided along with multi-modal training (Carlile, 2014; Särkämö et al., 2010). In parallel with the use of information on binaural abilities in stroke rehabilitation programs, personalized assistive algorithms could be designed, as suggested by Brown (2018). Spatial auditory cueing has already been shown to reduce unispatial neglect (Kaufmann et al., 2022; Schenke et al., 2021). Individualized algorithms could similarly enhance binaural cues or counteract shifts in auditory space to improve spatial perception as suggested by Brown (2018) for cochlear implant users.

The applicability of the MoBES procedure has brought the distant goal of individualized audiological diagnostics one step closer. The missing element regarding this procedure is a comprehensive model with few, but diagnostically relevant parameters. The most likely way to achieve this goal is to couple existing models of the different auditory stages from the auditory periphery, through the brainstem nuclei to the cerebral representations. A good starting point might be the work of Klug et al. (2020), who combined a well-established model of the auditory periphery with a functional count-comparison model of binaural interaction. However, their model does not include cortical processing stages. Once a comprehensive binaural hearing model is developed, algorithms such as the MoBES procedure can be of great help in characterizing the causes of individual hearing impairments. Moreover, because of its universal applicability, the MoBES procedure could also be used in the future for diagnostic measurements in various fields other than audiology.

5.5 Conclusion

The purpose of this work was to relate the underlying individual parameters or pathologies to differences in binaural perception. Exploring the longitudinal effects of ischemic stroke on binaural hearing revealed anomalies in many patients with clinically mild stroke symptoms. Impairments were mainly found in the acute, but also in the subacute, and chronic phases of stroke. Individual and lesion group-specific effects were identified in the acute phase of stroke, whereas the recovery of binaural hearing was found to be highly individual. In the future, the further developed model-based experiment steering procedure can be used to uncover the relationship between pathology and binaural perception and the underlying processes of such impairments in a more time-efficient manner. The next critical step is to construct a comprehensive model with few but diagnostically relevant parameters. Overall, this thesis highlighted the individual relation between stroke pathology and binaural perception. The findings underscore the need for efficient diagnostics and provide a foundation for the development of targeted interventions and support systems.

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