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Review article

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Clinical implications of brain asymmetries

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Abstract

No two human brains are alike, and with the rise of precision medicine in neurology, we are seeing an increased emphasis on understanding the individual variability in brain structure and function that renders every brain unique. Functional and structural brain asymmetries are a fundamental principle of brain organization, and recent research suggests substantial individual variability in these asymmetries that needs to be considered in clinical practice. In this Review, we provide an overview of brain asymmetries, variations in such asymmetries and their relevance in the clinical context. We review recent findings on brain asymmetries in neuropsychiatric and neurodevelopmental disorders, as well as in specific learning disabilities, with an emphasis on large-scale database studies and meta-analyses. We also highlight the relevance of asymmetries for disease symptom onset in neurodegenerative diseases and their implications for lateralized treatments, including brain stimulation. We conclude that alterations in brain asymmetry are not sufficiently specific to act as diagnostic biomarkers but can serve as meaningful symptom or treatment response biomarkers in certain contexts. On the basis of these insights, we provide several recommendations for neurological clinical practice.

Sections

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Key points

- Brain asymmetries — that is, structural and functional differences between the left and the right hemispheres — are a major source of interindividual brain variability.
- The substantial interindividual variability in brain asymmetry currently precludes its use as a diagnostic biomarker.
- Individual variability in brain asymmetry needs to be considered in the assessment of symptoms and treatment of various disorders.
- Altered brain asymmetries are observed in a number of neurological, neuropsychiatric and neurodevelopmental disorders.
- Brain asymmetries can act as meaningful symptom or treatment response biomarkers in a range of neurological contexts.
- Advancement of patient-tailored medicine will require clinical trials to elucidate how individual brain asymmetry influences the efficacy of lateralized interventions.

Introduction

Each human brain is unique, and interindividual variability is a crucial consideration when studying brain structure–function associations[1]. In clinical neurology, the rise of precision medicine, in which treatment approaches are tailored to individuals or subgroups of patients[2], has led to an increased emphasis on understanding brain variability and identifying relevant biomarkers[3–5]. One major source of this variability is left–right asymmetry in brain structure and function[6–8] (Fig. 1).

In the human brain, more than 90% of cortical and subcortical regions show structural asymmetry[9,10]. For example, the planum temporale, a brain region that overlaps with Wernicke's area and, thus, is relevant for language processing, shows a pronounced leftward volumetric asymmetry[11]. At the functional level, most people show left-hemisphere dominance for language processing[12] and manual praxis[13]. One consequence of these hemispheric differences is that aphasic language disorders and limb apraxia are more common and generally more pronounced and persistent following left-hemisphere damage than following right-hemisphere damage. The opposite holds for impairments in spatial orientation and extralinguistic communication and for visuospatial neglect[14]. Brain asymmetries are thought to increase processing efficiency and improve multitasking capabilities by avoiding bilateral interference[8,15]. They are complex and multifactorial (Box 1) and can change over the lifespan (Box 2).

In this Review, we provide an up-to-date overview of the clinical implications of brain asymmetries. We first summarize what is known about alterations in brain asymmetries in neuropsychiatric and neurodevelopmental disorders and specific learning disabilities. We focus on the results of meta-analyses and large-scale, multicentre empirical studies to ensure the robustness of the presented evidence. Keeping these findings in mind, we consider whether alterations in brain asymmetries can be used as diagnostic biomarkers for various disorders or disabilities. In addition, we discuss the implications of individual variability in brain asymmetry for neuropsychological deficits after focal brain injury and the role of brain asymmetries and laterality of onset for symptom variability in neurodegenerative diseases. In this context, we ask whether brain asymmetries can provide symptom biomarkers for cognitive, psychosocial and motor impairments after focal brain injury or neurodegeneration. We go on to highlight the importance of considering natural variability in asymmetric brain organization when administering lateralized neuromodulatory treatments and performing resective neurosurgery and discuss the potential of brain asymmetries as treatment outcome biomarkers. We conclude with an integrative discussion and propose directions for future studies on brain asymmetries in psychiatry and neurology, as well as providing recommendations for clinical practice.

Natural variability in brain asymmetries

The existence of functional lateralization in the human brain is well established[16], and handedness is the most commonly investigated manifestation of this phenomenon[13]. Two main methods are used to assess handedness: subjective report using multi-item hand preference questionnaires such as the Edinburgh Handedness Inventory[17], and objective hand skill measured with performance tests such as the pegboard test[18]. These tests allow the determination of a lateralization index, which indicates both the direction (left or right) and the strength or consistency of the asymmetry. On the basis of this index, individuals can be classified as left-handed, right-handed or mixed-handed. However, the boundaries of mixed-handedness remain vague and vary in the literature, so the categorization of handedness is often restricted to a left–right dichotomy[19]. Although the consistency of the hand preference of a person is likely to be a relevant mediator of handedness, we will focus mainly on the left–right direction of its manifestation. More covert manifestations of functional hemispheric asymmetries (for example, language, face perception or spatial attention) can be determined using behavioural tests such as the dichotic listening task[20] or divided visual field paradigms[21] and can also be assessed using electrophysiological methods such as EEG[22], neuroimaging techniques such as functional MRI (fMRI)[23] and neurophysiological techniques such as functional transcranial Doppler sonography[24].

Structural brain asymmetries are usually assessed at the macrostructural level, for example, in terms of volume or surface area of specific brain areas[10]. Typically, MRI is used to assess structural asymmetries in grey matter and diffusion-weighted imaging is used to assess structural asymmetries in white matter[25]. In addition, microstructural asymmetries – for example, in neurite distribution[26] – and asymmetries in gene expression and protein distribution can be assessed[27].

At the population level, a 'prototypical' pattern of hemispheric organization is observed whereby functions such as language, manual praxis and hand preference lateralize to the left hemisphere and functions such as spatial attention, emotional prosody processing and face recognition lateralize to the right hemisphere. However, there is crucial interindividual variability in functional asymmetry patterns, and various functions can sometimes be found in the 'atypical' hemisphere. For example, most people show leftward language lateralization, but the right hemisphere is dominant in some individuals; this phenomenon is also slightly more common in left-handers than in right-handers[28,29]. Around 95% of right-handers are estimated to exhibit left-hemisphere language specialization, but this percentage decreases to about 70% in left-handers.

Historically, whether other lateralized functions follow the same patterns as language has been unclear. Large-scale databases recording handedness and lesion side using standardized tasks are rare to find outside the language domain. This dearth of studies on non-language asymmetries is likely to reflect an implicit assumption of

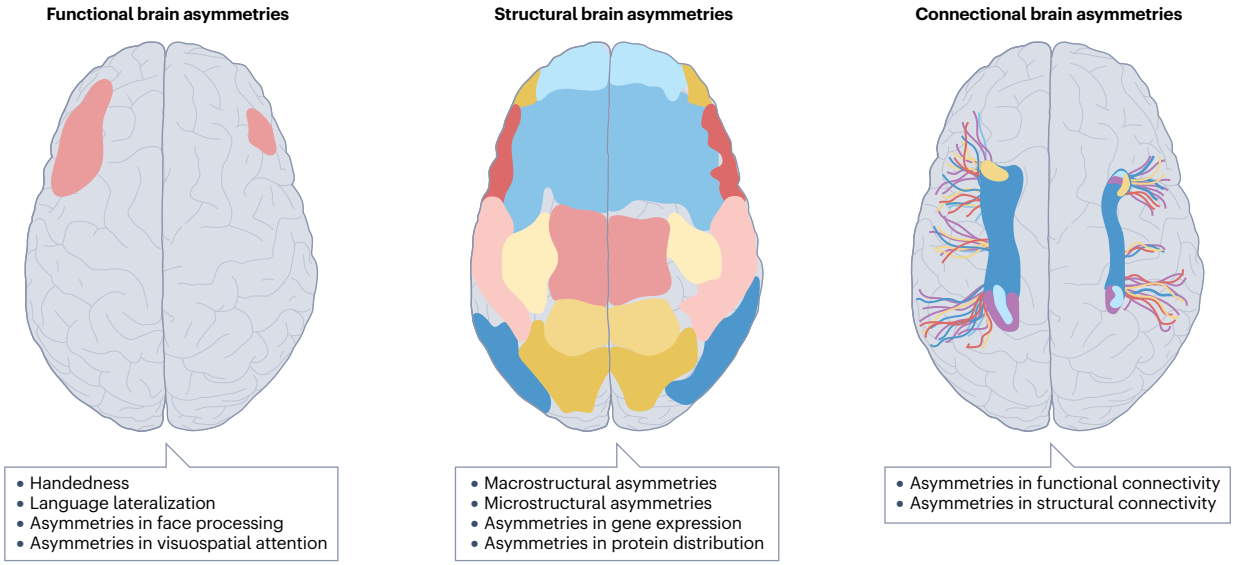

Fig. 1 | The three main forms of brain asymmetries. The left and right hemispheres show structural and functional differences in cortical and subcortical regions. These left–right differences manifest at the functional level, with handedness and language being lateralized to the left hemisphere and face processing and visuospatial attention being lateralized to the right hemisphere in most people. Asymmetries at the structural level include macrostructural and microstructural differences, as well as asymmetries in gene expression and protein distribution. In addition, the two hemispheres differ with regard to functional and structural connectivity.

complementarity of hemispheric specializations (Box 3). From this perspective, non-language functions would be expected to deviate from the typical hemisphere to the same extent as language[30], with around 5% of right-handers and 30% of left-handers having the function in the atypical hemisphere. However, such complementarity is not always the case, and research indicates that, in right-handers, the hemisphere that is dominant for non-language functions varies more than the hemisphere that is dominant for verbal or language functions (Fig. 2). For example, fMRI studies show that spatial attention tends to lateralize to the right hemisphere in ~80% of individuals, regardless of handedness[31–33]. Moreover, manual praxis shows lateralization to the left hemisphere in ~70% of left-handed and 80% of right-handed individuals[34,35]. When asymmetry for face and body selectivity was examined in left-handers and right-handers with verified left language dominance, 80% of the right-handers and 70% of the left-handers were found to process faces with the right hemisphere. For body selectivity, processing in the right hemisphere was observed in 94% of right-handers and 70% of left-handers[36].

In addition to the variability of functional hemispheric asymmetries, researchers explored the individual variability of structural hemispheric asymmetries. One study focused on individual variability in cortical surface area and cortical thickness associated with duplication of Heschl's gyrus in the left and right hemispheres[37]. The authors reported that in the left hemisphere, 66% of participants had a single Heschl's gyrus, whereas 23% showed duplication of the common stem and 11% showed complete duplication. In the right hemisphere, only 56% of participants had a single Heschl's gyrus, 22% showed duplication of the common stem and 22% showed complete duplication. Individual structural variability has also been described for the well-known leftward asymmetry of the planum temporale, which is present in 80% of the individuals[38]. Most large-scale studies on structural asymmetries, however, focus on group averages. Therefore, further investigation of individual variability in structural asymmetries will be an important priority for future research.

Altered brain asymmetries as diagnostic biomarkers

Biomarkers are an essential tool to fully capture the pathogenetic and symptomatic heterogeneity of neurological disorders within a precision medicine framework[3,39]. Many neuropsychiatric and neurodevelopmental disorders and specific learning disabilities have been linked to altered brain asymmetries[10,40], and it has been suggested that these altered brain asymmetries could be used as diagnostic biomarkers for disorders such as schizophrenia[41], depression[42] and attention-deficit hyperactivity disorder (ADHD)[43]. In this section, we review the empirical evidence for altered brain asymmetries in different groups of conditions.

Neuropsychiatric disorders

Brain asymmetries have been investigated in a wide range of neuropsychiatric disorders, with a particular focus on psychotic, mood and stress-related disorders[44]. Strong empirical evidence exists for alterations in functional and structural brain asymmetries in schizophrenia. At the functional level, robust evidence indicates that non-right-handedness — that is, left-handedness and mixed-handedness combined — is significantly more common in patients with schizophrenia than in healthy control individuals[45]. After controlling for biological sex, the prevalence of non-right-handedness was 1.5 times higher in patients with schizophrenia than in control individuals. A subsequent study on handedness as a biomarker in schizophrenia using 667 data sets from the FACE-SZ cohort found a high prevalence of both non-right-handedness (42.4%) and mixed-handedness (34.1%) in patients with schizophrenia[46]. In this study, mixed-handedness showed a significant correlation with positive schizophrenia symptoms.

Box 1

Origins of brain asymmetry: genes, environment and chance

As a prominent and immediately visible marker of human brain laterality, handedness has been central to exploring the roots of lateralization.

By introducing the idea that one of the alleles underlying handedness produces randomness, monogenic models of handedness have provided accurate predictions of familial and twin handedness patterns[122,123].

However, sufficiently powered genome-wide association studies were unable to identify a single gene that determined handedness; instead, the results suggested that at least 30–40 loci were associated with this trait[124,125]. As the ontogenesis of handedness is likely to result from a multistage process, any single defect in the chain of contributing genes might result in a similar outcome, explaining the apparently monogenic nature of polygenic inheritance[126].

The additive heritability effect of handedness seems to be modest and accounted for about one-quarter of the variance in a large international twin study[127]. Independent environmental influences that were reported in a large-scale population study included birthweight, multiple birth, season of birth, breastfeeding and sex, but even when taken together, these factors had only a subtle predictive effect on individual handedness[128]. Despite evidence that genes associated with handedness and language lateralization show only limited overlap[129], models similar to that of handedness have been proposed to forecast the probabilities of language dominance (and other lateralized cognitive modules) in the population[126]. Phenotypes of language dominance are more difficult to assess than handedness, but the limited data available roughly confirm the predictions of substantial variation in atypical lateralities in both left-handers and right-handers[126].

In summary, the hemispheric lateralization of brain functional modules seems to be determined by genetic, environmental and stochastic processes, although the precise mechanisms and their interactions remain to be clarified. Nevertheless, the seemingly modest contributing effect of each single factor results in a substantial and evolutionarily stable population bias of functional segregation in the brain. At the same time, the complex interplay of these factors gives rise to considerable and unpredictable variation in brain functional organization at the level of the individual.

In addition to handedness, a meta-analysis has shown that patients with schizophrenia show weaker language lateralization than healthy control individuals[47]. At the structural level, a large-scale study by the ENIGMA consortium found reduced thickness asymmetries in middle temporal brain areas in patients with schizophrenia, with 7% of the variance in asymmetry being explained by case versus control status[48]. These effects were driven by thinner left-hemispheric cortices in the patients.

With regard to depression, no case–control differences in handedness were observed in a meta-analysis of 87 studies[49]. Similarly, another meta-analysis found no evidence for an association between depression and EEG α-wave asymmetries[50]. A large-scale study by the ENIGMA consortium found no evidence for alterations in structural brain asymmetries in people with major depression[51].

In the case of post-traumatic stress disorder (PTSD), a meta-analysis showed a significantly elevated prevalence of non-right-handedness and mixed-handedness in patients with this condition[52]. Interestingly, a PTSD study in identical twins who were discordant for combat exposure found that co-twins of combat veterans with PTSD were more likely to be mixed-handed than were co-twins of combat veterans without PTSD, suggesting that mixed-handedness represents a familial risk factor for developing PTSD[53].

From a developmental perspective, studies have linked paediatric mental health difficulties to both left-handedness[54] and mixed-handedness[55,56]. Importantly, this phenomenon was observed at ages before the typical time of diagnosis for most neuropsychiatric disorders, suggesting a transdiagnostic link between brain asymmetries and neuropsychiatric disorders rather than a diagnosis-specific link.

Neurodevelopmental disorders

Altered hemispheric asymmetries manifest at both the functional and the structural levels in neurodevelopmental disorders such as autism spectrum disorder (ASD) and, to a lesser extent, ADHD and developmental language disorder (DLD).

At the functional level, a meta-analysis on resting-state fMRI data from seven datasets from the Autism Brain Imaging Data Exchange Project, totalling 370 people with ASD and 498 non-autistic control individuals, found robust evidence of atypical functional asymmetry in areas related to language, motor and perceptual functions[57]. These differences correlated with clinical measures of reciprocal social interaction, communication and repetitive behaviours. Further meta-analyses using handedness as a biomarker for functional asymmetries revealed that individuals with ASD were 3.48, 2.49 or 2.34 times more likely to be non-right-handed, left-handed or mixed-handed, respectively, compared with typically developing individuals[58].

A meta-analysis of data from 324 individuals with ADHD and 303 individuals without ADHD showed that those with ADHD had more rightward or less leftward asymmetry in spontaneous neuronal activity and temporal synchrony of the regional blood oxygen level-dependent signal than control individuals[59]. The findings on handedness in ADHD were less clear: although individuals with ADHD were 1.49 times more likely than control individuals to be non-right-handed, the evidence for elevated left-handedness and mixed-handedness among people with ADHD was very weak[60].

Structurally, individuals with ASD were found to display extreme rightward and leftward deviations in grey matter voxel-wise asymmetry compared with non-autistic male and female individuals, and the patterns of deviation were highly individualized[61]. This study leveraged the EU-AIMS Longitudinal European Autism Project[62], a large harmonized autism sample that was deeply phenotypically characterized. A further study focused on cortical thickness data from 1,455 individuals with ASD and 1,560 control individuals across 43 independent datasets from the ENIGMA consortium and revealed significantly altered average asymmetry of networks involving the fusiform, rostral middle frontal and medial orbitofrontal cortices[63]. These findings align with those of a previous study by the ENIGMA consortium, in which an analysis of data from 1,774 individuals with ASD and 1,809 control individuals from 54 independent datasets revealed altered structural brain asymmetry

in ASD[64]. Structural variability was shown to be lower than functional variability in people with this condition[57].

Findings on structural brain asymmetry in ADHD are less definitive. In the largest study on structural asymmetries in ADHD to date, asymmetry of subcortical and cortical structures in 1,933 people with ADHD and 1,829 unaffected control individuals was analysed[65]. Separately conducted analyses for children, adolescents and adults showed that any asymmetry differences were small. Only differences in globus pallidus asymmetry in adults were statistically significant, with a false discovery rate of <0.05, and none of the effects survived study-wide correction for multiple testing. However, He et al.[59] found global and more leftward or less rightward asymmetry of brain structure and function in people with ADHD compared with healthy control individuals, providing a strong structural basis for the functional asymmetry in ADHD. They also found that ADHD symptom measures were positively correlated with absolute asymmetry, that is, more severe ADHD symptoms were associated with higher absolute asymmetry. Overall, large-scale studies and meta-analyses strongly support the presence of altered brain asymmetries in ASD, but the existence of similar effects in ADHD is still under debate.

Childhood-onset fluency disorder (also known as stuttering) is another neurodevelopmental disorder in which evidence for brain asymmetry is inconsistent[44]. For example, a meta-analysis of 52 studies failed to find conclusive evidence of differences in handedness between individuals who stuttered and control individuals[66].

The idea that atypical language dominance is a risk factor for DLD seems intuitive, but a large-scale Doppler study[67] did not find elevated rates of atypical speech dominance in children with DLD. However, a follow-up study revealed that individuals with DLD were more likely to demonstrate inconsistent lateralization between language tasks (for example, left dominant for semantic processing versus right dominant for phonological processing) than healthy control individuals[68]. Therefore, a 'fractured' language system might be a risk factor for DLD.

Specific learning disabilities

Altered hemispheric asymmetries have been identified in the context of specific learning disabilities, although the findings are inconsistent. Specific learning disabilities are characterized by persistent difficulties in reading, writing, arithmetic or mathematical reasoning skills during the years of formal schooling that are not better explained by developmental, neurological, sensory or motor disorders[69]. The main types are dyslexia (difficulties with reading and spelling), dyscalculia (difficulties in understanding numbers) and dysgraphia (difficulties with writing). Of these three conditions, dysgraphia has been the least studied with respect to brain and behavioural asymmetries.

Two meta-analyses published in 2023 (refs. 70,71) indicated reduced activity in the right anterior intraparietal sulcus and increased activity in the right insula in individuals with dyscalculia compared with control individuals. However, both of these meta-analyses have been criticized for including studies that had small sample sizes, typically assessed a single cognitive task and lacked consensus on the operational definition of dyscalculia[72]. No brain differences between 30 children with dyscalculia and 38 control individuals were found in a recent fMRI study[72]. Similarly, a meta-analysis of 22 studies found no differences in handedness between individuals with dyscalculia and control individuals[73].

The bulk of research on brain asymmetries in specific learning disabilities has been carried out in people with dyslexia, and the evidence suggests that this condition is associated with reduced leftward asymmetries of temporal and possibly frontal language areas[44,74,75]. A systematic review of 49 studies on the EEG correlates of dyslexia reported differences in left temporoparietal sites between children with dyslexia and control individuals during reading-related tasks[76]. A multimodal meta-analysis showed convergent structural and functional alterations in the left superior temporal gyrus in dyslexia[77]. However, an activation likelihood estimation meta-analysis of diffusion tensor imaging studies showed no reliable clusters underlying differences between individuals with dyslexia and control individuals after correcting for multiple comparisons[78]. Moreover, another study failed to find differences in grey matter volumes of cortical and subcortical structures in 31 individuals with dyslexia versus 41 control individuals[79]. A large-scale meta-analysis of 68 studies on handedness and dyslexia revealed a robust – albeit of small effect size – association with mixed-handedness[80], suggesting that the degree and not the direction of asymmetry could be the variable of interest.

Box 2

Ontogeny of brain lateralization: changes over the lifespan

From prenatal stages to old age, the hemispheric lateralization of the brain evolves in a multifaceted manner. Several anatomical and functional hemispheric asymmetries manifest early in human development, with some structural asymmetries already observable in utero[130]. As early as the 23rd week of gestation, a leftward folding asymmetry becomes apparent in the depth of the Sylvian fissure, which hosts the planum temporale.

Multiple structural asymmetries are present at birth[131,132], some of which persist into adulthood whereas others are thought to be more dynamic and to change during development[133]. As children advance into adolescence, brain asymmetry for various structures and functions is thought to increase. In young children, the language system is believed to exhibit a fairly symmetrical distribution across both hemispheres. However, as language development progresses, a gradual shift occurs towards specialization in one hemisphere[134]. Similarly, face processing is thought to develop from an initial bilateral system to become more right hemispheric, potentially influenced by competition for functional space with areas specialized for reading[135]. These systems are thought to reach a stable state of lateralization in early adulthood.

Numerous studies suggest a decline in functional hemispheric asymmetry in the later stages of life, possibly related to structural changes or neural atrophy[95,136]. Two models have been put forward to account for this reduction in asymmetry: the right hemi-ageing model proposes that the right hemisphere is more vulnerable to ageing effects than the left hemisphere, resulting in increased right-hemisphere impairment[137], whereas the hemispheric asymmetry reduction in older adults model posits a reduction in functional hemispheric lateralization in the prefrontal cortex with age[138]. Both models have received some support and do not seem to be mutually exclusive.

In conclusion, the most reliable evidence on brain asymmetries in specific learning difficulties has been found for dyslexia, especially concerning functional as opposed to structural asymmetries.

Altered brain asymmetries as symptom biomarkers

The findings discussed in the previous section suggest that brain asymmetries hold limited value as diagnostic biomarkers for various reasons. First, similar altered asymmetries, for instance, in hand preference, are associated with different disorders, making them highly nonspecific as differential diagnostic biomarkers. Second, although the more specific alterations, such as atypical structural or functional brain asymmetries that seem to be linked to pathognomonic signs or symptoms, are promising, they require complex and technical diagnostic procedures and their applicability to individual patients remains to be evaluated. Third, as healthy individuals can also present with altered brain asymmetries, atypical asymmetries might be of limited use as cardinal diagnostic biomarkers. Nevertheless, altered brain asymmetry could provide a meaningful addition to multifactorial prediction models for conditions that are associated with specific alterations of brain asymmetries, such as schizophrenia and ASD.

Diagnosis is not the only application for biomarkers[39], and evidence suggests that altered brain asymmetries might be more meaningful as biomarkers of specific symptoms than for differential diagnosis. For example, associations of altered brain asymmetries with specific neurodevelopmental features have been reported[81]. The idea of brain asymmetries as symptom biomarkers is especially relevant for focal brain injuries and neurodegenerative disorders, as we discuss in this section.

Neuropsychological deficits after focal brain injury

Textbook descriptions of neuropsychological symptomatology readily distinguish between left-brain and right-brain stroke. Consistent with the patterns of hemisphere specialization that are observed in the healthy population, disorders of language and manual praxis are more common and generally more pronounced and persistent following left-hemisphere damage, whereas right-hemisphere damage is associated with impairments in spatial orientation, spatial attention and extralinguistic communication[14]. However, these conventional asymmetry–symptom associations are far from universal. For example, reports of right-sided aphasia or apraxia in left-handers and, more rarely, right-handers exist in the literature[82].

Given the substantial individual variability in functional hemispheric segregation, 'unusual' comorbid impairment of cognitive domains associated with opposite hemisphere dominance should be quite common. Speech and spatial cognition dominantly cohabit in the same hemisphere in about 25% of right-handers and 30% of left-handers[32] (Fig. 3). Although these functions are subserved by distinct neurocognitive networks, when they crowd in the same hemisphere their networks partially overlap and share an arterial blood supply. Accordingly, focal brain damage, such as stroke, would be expected to simultaneously disrupt both networks, causing concurrent aphasia and spatial dysfunction (see Fig. 3 for examples). This reasoning was supported by an analysis of concurrent aphasia and spatial disability (defined as spatial agnosia, spatial dysgraphia, loss of topographic memory or visuospatial neglect) in 270 survivors of unilateral stroke[83]. Comorbidity was observed in 9% of the right-handed and 34% of the left-handed patients. In line with observations of crowding between speech and spatial attention in the intact brain[32], comorbidity was more than twice as likely following left-sided than right-sided stroke regardless of patient handedness.

More recent research on post-stroke comorbidities examined patients with specific lesion sides and/or neuropsychological deficits. For example, a review in right-handed individuals with aphasia caused by a right-hemisphere lesion, also known as crossed aphasia, found visuospatial neglect symptoms in 58% of cases[84]. This finding is consistent with functional imaging data from the healthy brain: only about 20% of right-handers with atypical language laterality also have reversed visuospatial attention[32]. Thus, crossed aphasia often pairs with visuospatial neglect. In another study of 11 patients (10 right-handed and 1 ambidextrous) with left-hemisphere stroke diagnosed with visuospatial neglect, all but one (91%) also had aphasia[85]. This finding is agreement with observations in the brains of healthy right-handers, in whom atypical dominance for spatial attention is rarely accompanied by transposition of speech[32].

Box 3

Mechanisms of hemispheric functional segregation

The statistical hypothesis suggests that functions lateralize according to innate biases of independent sources and, thus, that atypical lateralization of one function will have no consequences for the lateralization of other functions. This hypothesis is supported by the absence of correlations between asymmetries of language and spatial functions, suggesting that functional segregation exists only by virtue of the innate sources that direct its laterality[83]. Alternative models propose a more causal mechanism of functional segregation, in which strong innate biases also prevent complementary functions from crowding in the same hemisphere[139]. Low-to-moderate but nevertheless significant correlations between the laterality indices of some but not all functions were found in a larger and more elaborate study, which suggested complementarity for some but independence for other pairs of functions[31]. Most of the current data seem to support a predominantly statistical pattern of segregation, as it allows for the crowding of functions that occurs in a substantial proportion of the general population and is more difficult to explain by a causal mechanism[30].

The observation of a completely reversed brain functional phenotype (mens inversus totalis or 'inverted mind'), which is present in about 10% of left-handers and features atypical lateralization of all probed cognitive localizers (language and praxis in the right hemisphere and spatial attention, face recognition and emotional prosody in the left hemisphere)[34], suggests the existence of an innate blueprint before the ontogenesis of hemispheric differentiation that shows a prominent population bias towards typical functional segregation but occasionally gives rise to a mirrored building plan, leading to individuals with complete functional reversal, including handedness[14]. People with reversed visceral organization (situs inversus totalis) do not show the reversed brain phenotype as, unlike in some vertebrates, the mechanisms for visceral and brain functional asymmetry seem to be unrelated in humans[140].

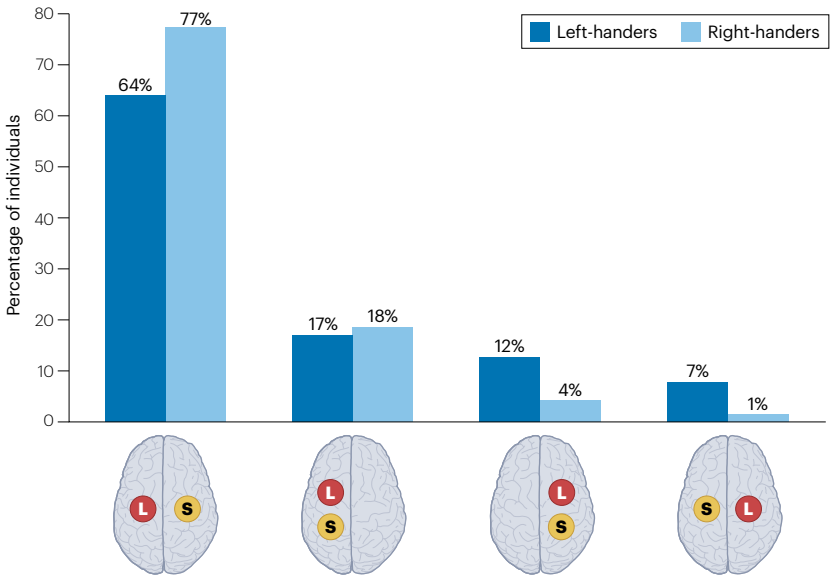

Fig. 2 | Variability in hemisphere organization in the general population. Neuroimaging research indicates that hemispheric organization is more variable than was traditionally assumed. For example, every different combination of left and right hemispheric dominance for language (L) and spatial attention (S) has been observed irrespective of handedness, although some patterns are more common than others. This bar chart visualizes the rates of each pattern observed in left-handers and right-handers and is based on a meta-analysis of imaging studies of neurologically healthy volunteers published in 2022 (ref. 32).

Other atypical clinical presentations have been seen after unilateral stroke. For example, visuospatial and ideomotor apraxic deficits have been reported in 22% of right-handed patients after right-sided stroke, even though those functions usually localize to opposite hemispheres[86]. Individual differences in hemisphere segregation might also explain unexpected absence of comorbidity. For example, aphasia and limb apraxia often co-occur after a middle cerebral artery stroke, but reports exist of a dissociation between these deficits despite extensive brain damage within the middle cerebral artery territory[82]. Such cases could arise from opposite hemisphere dominance for language and manual praxis, which, according to a recent fMRI study, is present in 13% of right-handers and 42% of left-handers, mostly because of straying of praxis to the right hemisphere[32,35].

Considering the extensive interindividual differences in hemispheric segregation, neuropsychological assessment after unilateral brain damage should go beyond lesion laterality in both left-handers and right-handers. Similarly, the outcome of presurgical assessment of hemisphere dominance for language should not be taken as evidence for typical or atypical dominance of non-examined cognitive functions.

Laterality of onset in neurodegenerative diseases

Relationships between brain asymmetries and laterality of symptom onset are evident in neurodegenerative disorders such as Alzheimer disease, Parkinson disease, multiple sclerosis and amyotrophic lateral sclerosis. Brain asymmetries might be a symptom biomarker for cognitive and motor impairments in such conditions.

Laterality of symptom onset is most pronounced in Parkinson disease: unilateral motor symptom onset and arm swing asymmetry are often visible before the clinical diagnosis and, thus, are reliable biomarkers in clinical practice. Motor symptoms show a slight bias towards the side of the dominant hand, with 59.5% of right-handed patients presenting with right-dominant symptoms and 59.2% of left-handed patients presenting with left-dominant symptoms[87]. Patients with right-sided motor symptom predominance typically experience problems with language-related tasks and verbal memory, whereas patients with predominant left-sided motor symptoms are more likely to show impairment on tasks involving spatial attention, visuospatial orientation and memory and mental imagery[88]. Patients with left-dominant motor symptoms frequently show anxiety and depressive symptoms[89], whereas patients with right-dominant motor symptoms more often present with psychotic symptoms[90] and sleep behaviour disorders[91]. The effects of lateralized brain alterations on motor and non-motor outcomes in people with Parkinson disease have also been explored. A multicentre study of right-handed patients revealed a link between asymmetric dopaminergic loss in the nigrostriatal pathway and Parkinson disease symptoms, with left-hemispheric loss resulting in cognitive impairments and right-hemispheric loss being associated with increased motor severity[92]. Moreover, patients with Parkinson disease with right-sided symptom onset show more severe white matter damage than those with left-sided onset[93], indicating that asymmetric neurodegeneration could be a predictive biomarker for side of onset and type of symptoms.

Patients with Alzheimer disease can show either impairments in verbal memory and language or visuospatial deficits, depending on which hemisphere has the greater neurodegeneration and amyloid-β pathology[94]. A large longitudinal study demonstrated a loss of leftward asymmetry in the frontal and anterior temporal cortex and a loss of rightward asymmetry in the insular and lateral temporoparietal regions during healthy ageing. This reduction in naturally occurring hemispheric asymmetry is accelerated in Alzheimer disease[95] and might, thus, have predictive value. When interhemispheric differences in tau distribution were analysed, 70% of patients with Alzheimer disease showed an asymmetric distribution, with no overall side bias. This asymmetry was linked to an earlier age of disease onset and more severe pathology[96]. However, the intriguing finding that asymmetric neurodegeneration can be used as a symptom biomarker is not robustly reflected in behavioural markers such as an altered prevalence of handedness[97].

Side of onset is also a relevant symptom biomarker in multiple sclerosis: at disease onset, patients present with unilateral limb weakness, and asymmetric impairments in aerobic muscle function such

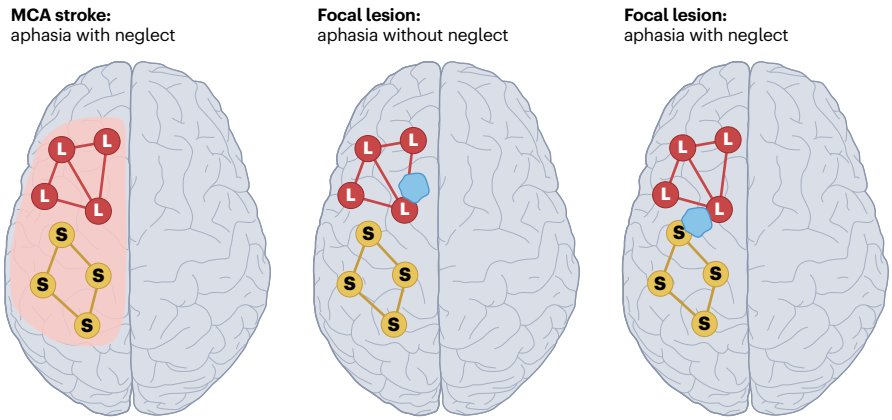

Fig. 3 | Hemisphere crowding and cognitive impairment comorbidity. Traditionally, brain lesions were not expected to cause comorbid aphasia and neglect, as language (L) and spatial attention (S) were assumed to lateralize to opposite hemispheres. However, subsequent research has shown that crowding of these functions in the same hemisphere is quite common in the healthy brain, so comorbid aphasia and neglect should not be particularly rare. When crowding is present, such comorbidity could result from a stroke of the middle cerebral artery (MCA), which supplies blood to critical nodes of both the L and S networks, or when a focal lesion affects both networks.

as lower-limb strength, aerobic performance and metabolism during exercise are also observed[98]. Asymmetric corticospinal excitability was also shown to predict the severity of physical and cognitive symptoms in patients with multiple sclerosis: the hemisphere linked to the weaker hand showed greater excitability than the other hemisphere in the early stages of the disease, and a subsequent shift to increased excitability in the hemisphere linked to the stronger hand predicted more severe symptoms[99].

Research on onset laterality in amyotrophic lateral sclerosis is still a developing field with few published findings, but the available data suggest that brain asymmetry could be a predictive symptom biomarker. Patients initially present with unilateral limb weakness that typically affects the dominant limb and worsens on the body side of symptom onset during disease progression. For limb-onset symptoms, rates of 64–70% have been reported for concordance between the side of onset and handedness[100]. For example, muscle twitching is most pronounced in the limb muscles and most intense in the muscles of the dominant hand, with the greatest differences being observed in patients with upper limb onset[101], reinforcing the potential utility of handedness as a symptom biomarker.

Asymmetric neurodegeneration might also be a reliable biomarker to distinguish between disorders. For example, a meta-analysis showed that pronounced atrophy was evident in the left putamen in patients with Huntington disease, in the right hippocampus in patients with mild cognitive impairment and in the left hippocampus in patients with Alzheimer disease, but no consistent asymmetric pattern was found in Parkinson disease[102]. Taken together, the findings to date suggest that brain asymmetries of neurodegeneration and laterality of symptom onset could be useful as symptom biomarkers for cognitive and motor impairments in neurodegenerative diseases.

Hemispheric asymmetries as treatment response biomarkers

In addition to predicting the symptoms that patients are likely to experience as a result of focal unihemispheric brain damage or neurodegeneration, brain asymmetries could constitute meaningful biomarkers to predict the response to lateralized neuromodulatory treatments and resective neurosurgery.

Lateralized neuromodulatory treatments

Neuromodulation has become a viable treatment option for a wide array of brain-related disorders, including mood disorders, chronic pain, neurodegenerative diseases and epilepsy[103]. The working principle of neuromodulation is to suppress or enhance activity within targeted brain regions or networks to rectify dysfunctional neuronal activity. Many established neuromodulation protocols are lateralized, either because they target one specific hemisphere or because they modulate the two hemispheres in different ways. In some protocols, the selection of the targeted hemisphere is personalized on the basis of asymmetries in clinical symptoms and/or pathological features. For example, although simultaneous bilateral deep brain stimulation is the usual approach to surgically improve motor functioning in Parkinson disease, some centres perform staged unilateral deep brain stimulation in patients with predominantly one-sided motor symptoms, initially limiting the implantation to the most affected hemisphere[104].

Many lateralized neuromodulation procedures lack validation of an individualized approach to choosing the side of the brain to be targeted. For example, the established non-invasive brain stimulation (NIBS) protocols for treating individuals with mood disorders, such as refractory major depressive disorder or anxiety disorders, typically aim to upregulate the activity of the dorsolateral prefrontal cortex (DLPFC) in the left hemisphere specifically, sometimes in combination with inhibitory transcranial magnetic stimulation of the right DLPFC[105,106]. The rationale of this approach is to restore a hemispheric imbalance caused by a hypoactive left DLPFC, which is commonly observed in depressive and anxiety disorders and is believed to reflect disturbances in emotional regulation and approach–withdrawal motivation[105]. This approach works on the assumption that the hemispheric implementation of the modulated function is identical in every patient, which seems highly unlikely considering the vast variability observed in functional brain asymmetries. However, the effects of individual differences in hemispheric organization on NIBS efficacy for the treatment

of mood disorders have not yet been investigated. Analogous to right-hemisphere language dominance, the underlying functions that serve as the target for NIBS are likely to be reversed in some individuals, meaning that the stimulation procedure must also be reversed to be successful.

The lack of personalized selection of the hemisphere for stimulation could partially explain why NIBS does not always produce remission of depression. With the advent of neuroimaging-based protocols to facilitate individualized targeting of NIBS, such as the SAINT protocol recently approved by the FDA for depression treatment, research to consider between-patient differences in hemispheric organization as a determinant of stimulation laterality should be prioritized[106]. More generally, we advocate that future studies exploring the application of neuromodulation to treat other brain disorders should be mindful of how individual variability in hemispheric asymmetry might factor into the selection of the stimulation target.

Resective neurosurgery

The clinical relevance of individual functional brain asymmetries as treatment response biomarkers is probably best recognized in the management of epilepsies. Strong evidence indicates that in patients with longstanding epilepsy, brain representations of cognitive functions can reorganize to regions where they are not usually seen in neurotypical control individuals. Altered organization of language and memory networks has been demonstrated, generally consisting of recruitment of regions of the healthy hemisphere, for example, shifting of language representation to homotopic contralateral regions in patients with early-onset left temporal lobe epilepsy or left-hemisphere adaptations to increase visual memory performance in patients with right temporal lobe epilepsy[107–110]. Considering reorganization merely as a shift to bilateral or contralateral reorganization does not do justice to the complexity of the cognitive system, however. For example, language is not a monolithic function, and atypical representation may be observed for some skills (for example, reading) but not for others (for example, speech) in the same patient[111,112]. In addition to the assumed adaptive plasticity of the brain to ictal and interictal activity, seizures cause widespread disruptions of neural connectivity patterns that give rise to remote and diffuse effects, which can lead to neurocognitive deficits outside the epileptogenic region[113,114]. Diffuse cognitive dysfunction is not limited to generalized tonic–clonic and absence seizures and has also been demonstrated in focal epilepsy syndromes[115]. Epilepsy-induced reorganization of cognitive networks and adverse effects on remote pathway connections result in high variability of the cognitive profile in individual patients with epilepsy, which complicates neuropsychological identification of lateralized and focal brain impairment and should be considered in personalized treatment approaches for intractable epilepsy.

Improved seizure control is the main objective for epilepsy surgery, but preservation of cognitive function is also important. In resective surgery, the risk of inducing cognitive impairment must be weighed against the competing need to maximize the removal of potential epileptogenic tissue. The temporal and frontal lobes, which are associated with neural representations of memory and language, are most vulnerable to epileptogenesis. Patient H.M., who developed global amnesia following bilateral medial temporal lobe resection to control seizures, was a pivotal case for our understanding of the role of the hippocampus in amnesia and episodic memory[116]. The tragic outcome of H.M. terminated the use of bilateral hippocampal ablation and prompted functional assessment of the ipsilesional and contralesional hippocampus through the intracarotid amobarbital procedure (IAP) when planning unilateral resections. Originally designed to determine hemispheric language dominance, the IAP was adapted to screen for the risk of postoperative amnesia in candidates for temporal lobe resection[117,118]. In this procedure, each cerebral hemisphere is anaesthetized in turn by injecting sodium amobarbital into a single internal carotid artery through a femoral catheter. The drug causes transient hemiplegia and, if the injection is in the language-dominant hemisphere, speech arrest and dysphasia. The patient is shown stimuli before and after the injection to assess memory performance of each hemisphere separately. Intact memory performance following injection of the diseased hemisphere indicates a limited risk of post-surgical amnesia, although postoperative material-specific memory deficits remain likely[119]. Owing to concerns about the reliability and validity of the IAP, the use of this invasive procedure has recently been reduced without adverse effects on surgical outcomes[120].

To minimize language deficits after surgery, careful delineation of the epileptogenic region surrounding the epileptic focus by imaging and electrocorticography, as well as the identification of eloquent functional brain regions through functional neuroimaging and/or during awake neurosurgery, are important aspects of surgical decision-making. Postoperative intrahemispheric and interhemispheric reorganization of language activation patterns has been described, which seems to depend on the side of surgery and the degree of seizure control that is achieved[108,121].

Conclusions and future directions

On the basis of the evidence that we have reviewed in this article, we conclude that from a clinical perspective, brain asymmetries can be used as meaningful symptom and treatment response biomarkers but not as diagnostic biomarkers at present.

The literature on brain asymmetries in psychiatric and neurodevelopmental disorders provides substantial empirical evidence for an increased prevalence of atypical functional and structural asymmetries in several disorders and disabilities. Importantly, however, atypical brain asymmetry is not currently a sensitive biomarker for the differential diagnosis of any of the conditions that we have discussed. The poor pathognomonic specificity of the most accessible indicators of brain asymmetry, such as handedness, and the relatively high prevalence of atypical behavioural and brain asymmetries in the healthy population limit the diagnostic value of atypical brain asymmetries for the individual patient. That said, however, brain and behavioural asymmetries might prove to be useful in multifactorial prediction models or for disorders in which the prevalence of atypical asymmetry is linked to cardinal signs and symptoms. Although some evidence suggests that such indicators exist, for example, in schizophrenia and ASD, their clinical relevance remains to be evaluated.

In contrast to their limited usefulness as diagnostic biomarkers, brain asymmetries can be predictive of the manifestations and nature of symptoms that patients are likely to experience following focal unihemispheric brain damage or neurodegeneration. Moreover, we argue that brain asymmetries can act as meaningful treatment response biomarkers that should be considered when administering lateralized neuromodulatory treatments and performing resective neurosurgery. Importantly, to ensure optimal treatment, individual variability in asymmetric brain structure and function must be determined for each patient, even in cases in which atypical functional hemispheric specialization seems unlikely.

We believe that the research findings that we have discussed in this Review have important implications for clinical practice and future treatment approaches within a personalized medicine framework in neurology. With these findings in mind, we provide four recommendations for future clinical practice. First, assessment of behavioural preferences (for example, handedness) and functional hemispheric asymmetries (for example, language lateralization) should aid our understanding and prediction of associated symptoms in individual patients. Second, clinical examination of cognitive functions should include not only the functions that are prototypical for the damaged hemisphere (for example, assessment of language functions after left-hemispheric stroke) but also those prototypical for the other hemisphere, as both left-handed and right-handed individuals can deviate from typical hemispheric segregation. Third, in the case of neurodegenerative diseases, monitoring which hemisphere is more strongly affected could help us to tailor therapeutic interventions and resource activation strategies more effectively; for example, in a patient with faster progression of neurodegeneration in the left than in the right hemisphere, non-verbal resource activation strategies might be more helpful than verbal resource activation strategies. Finally, when using lateralized interventions aimed at modulating brain regions or removing diseased brain tissue, we should be mindful of how individual variability in hemispheric asymmetry can alter the functional relevance of the targeted brain area. Pre-treatment evaluation of the hemispheric dominance of relevant cognitive modules is recommended.

In addition to these suggestions for clinical practice, the approach that we have presented in this Review also has implications for clinical laterality research. Although increasing numbers of laterality studies are being performed in samples of thousands of participants or more, their usefulness will continue to be limited if only the most accessible indicators of brain asymmetry, such as handedness, are analysed in relation to case versus control status for disorders. Instead, we propose that multifactorial asymmetry phenotypes that reflect a broader range of hemispheric asymmetry patterns should be mapped to symptom severity in functionally relevant symptom clusters, as well as to treatment response.

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S.O. conceptualized the article. S.O. conceptualized one figure, R.G. created two figures and G.V. and E.M.K. created the boxes. All authors researched data for the article, contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

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