Handedness and Anatomical and Hemodynamic Asymmetries of the Carotid Arteries

Anica Jansen van Vuuren- JNSANI001

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COMPULSORY DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced.

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Abbreviations

A_{MEAN}	-	Mean artery angle
A_{SUM}	-	Accumulative artery angle
BP	-	Blood pressure
BT	-	Brachiocephalic trunk
CCA	-	Common carotid artery
CTA	-	Computed tomography angiography
DEV_{MEAN}	-	Mean angle deviation from vertical
DEV_{SUM}	-	Accumulative angle deviation from vertical
D_{MAX}	-	Maximum diameter
D_{MIN}	-	Minimum diameter
ECA	-	Common carotid artery
ICA	-	Internal carotid artery
LCCA	-	Left common carotid artery
LECA	-	Left external carotid artery
LICA	-	Left internal carotid artery
LQ	-	Laterality quotient
LSA	-	Left subclavian artery
RCCA	-	Right common carotid artery
RCCA-BT	-	Combined right common carotid artery and brachiocephalic trunk
RECA	-	Right external carotid artery
RICA	-	Right internal carotid artery
RSA	-	Right subclavian artery

TI	-	Target index
V_{DIA}	-	Peak diastolic velocity
V_{MEAN}	-	Mean velocity
V_{SYS}	-	End systolic velocity

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Abstract

Asymmetry in the vasculature arising from the human aortic arch seems the obvious place to look for an anatomical basis for lateralized cerebral functions, but this relationship has never systematically been investigated. This study explored the relationship between handedness and the anatomical and hemodynamic characteristics of the carotid arteries, analysing potential asymmetries between the left and right common, internal and external carotid arteries in left-handed versus right-handed individuals. The study is separated into two chapters: geometric (n = 199) and hemodynamic (n = 234). A revised version of the Edinburgh Handedness Inventory classified all participants into relevant handedness preference categories. For the geometric study, detailed measurements of the common carotid arteries in computed tomography angiography scans were obtained using Radiant DICOM Viewer (64-bit) imaging software. Selected geometric parameters of the vessels measured included minimum, mean, and maximum diameters, length, angle and calculated resistance to blood flow. Cases of unconventional branching patterns were analysed separately. For the hemodynamic study, Speed and Accuracy Target Tests quantified the participants' handedness performance. Doppler ultrasound was performed using the Vivid i GE Ultrasound system, on the common, internal and external carotid arteries. Hemodynamic parameters of the Doppler waveform were recorded, including Peak systolic and end-diastolic velocity, Resistive index, Pulsatility index, volume flow rate, and vessel diameter. The data was analysed with mixed design ANOVAs, discriminant function analyses, multiple regressions, and paired and independent t-tests, to investigate the asymmetries and predictive properties of the measured variables. The findings revealed that the extracranial vasculature feeding the cerebral hemispheres are asymmetrical in a direction that decreases blood flow to the hemisphere non-dominant for handedness. This implies greater resting perfusion of the hemisphere dominant for handedness.

Keywords: handedness, cerebral lateralisation, common and internal carotid arteries, arterial geometry, arterial hemodynamics, artery asymmetry.

Handedness and Anatomical and Hemodynamic Asymmetries of the Carotid Arteries

Handedness is the most obvious behavioural expression of lateralised cognitive function. Despite the wealth of data on handedness and cerebral lateralisation the mechanisms underpinning handedness have yet to be determined (Amunts, Jancke, Mohlberg, Steinmetz, & Zilles, 2000).

Although asymmetric cerebral perfusion at rest, as well as during motor and cognitive function has long been established in the literature, we argue that these asymmetries are already evident at the level of the core extracranial arteries supplying the brain. The aim of this study is to empirically assess the relationship between handedness (as an indirect indicator of hemispheric lateralisation) and asymmetries in the branches of the aortic arch.

This is a continuation of a pilot study conducted in 2012, submitted in partial fulfilment of the requirements for the award of the degree of BSoc Sci Hons Psychology at the University of Cape Town. The findings of the pilot study provided a strong motivation for the current dissertation which significantly expanded the analysis.

In order to systematically explore the handedness-blood flow relationship, two separate but complementary studies were designed and conducted. These studies addressed the question at both anatomical and physiological levels. The geometric study (Chapter 2) assessed the structural characteristics of the common carotid arteries (CCAs). This study compared geometric characteristics of the large calibre arteries that eventually feed the left and right cerebral hemispheres – namely lumen diameter, length, and angle deviation. With these measures, the resistance within each artery could be calculated.

The hemodynamic study (Chapter 3) assessed the hemodynamic characteristics within the CCAs, internal carotid arteries (ICAs) and external carotid arteries (ECAs). This allowed for accurate real-time measures of arterial diastolic and systolic velocities, flow velocities, resistance and pulsitility indices and blood volume flow rates within the vessels. It also satisfied a geometric component through diameter measures of the CCAs, ICAs, and ECAs, taken 2cm from the bifurcation — an important variable the first study could not account for.

Both hand preference and hand-proficiency were assessed in this dissertation. The assessment of hand-proficiency placed the participants’ handedness on a continuum, thereby addressing the subtle degrees of lateralisation.

Despite the impossibility of determining the direction of causality of the handedness-blood flow relationship on the basis of the studies conducted here, the empirical investigation of this relationship warrants investigation because of its intrinsic interest and relevance to neuropsychology research and practice. By learning more about the mechanisms that underlie these relationships, we may throw additional light on a wide range of neuropsychological issues.

Chapter 1: Literature Review

A fundamental unanswered question in modern neuroscience is the biological basis of cerebral lateralisation — whereby manual dexterity, language and spatial cognition are distributed across the hemispheres in a regular asymmetrical pattern (Carmon & Gombos, 1970; Jansen et al., 2006). Although it is partially reflected by minor morphological differences between the two hemispheres, the physical mechanism of this striking asymmetry is still not understood (Amunts et al., 2000; Josse et al., 2008). Handedness interacts with a number of other variables — including sex, age, culture, family history, writing posture, and asymmetries in the blood supply to the extremities — but none of these studies have identified the actual mechanism whereby cerebral lateralisation occurs (Amunts et al., 2000; Hannay, 1988; Herve et al., 2006; Sommer et al., 2008; Thilers et al., 2007; Vuoksimaa et al., 2009).

Blood flow to the brain is closely associated with metabolic requirements of the tissue for glucose and oxygen (Siesjo, 1978). However, large increases in flow are necessary to produce small increases in oxygen metabolic rates. Buxton and Frank (1997) approximate the required flow increase to be 19% for a 5% enhancement in localised cerebral oxygen metabolism.

The large arteries supplying the two cerebral hemispheres branch asymmetrically from the aortic arch and are highly variable in their geometric features. It is also well established that greater perfusion of the hemisphere dominant for handedness occurs at rest, during motor control and during verbally mediated cognition (Klingelhöfer et al., 1997; Luczywek et al., 2003; Willis et al., 2002). Since these tasks create greater metabolic demand in the hemisphere concerned, it may be assumed that asymmetric cerebral perfusion is an effect rather than a cause of the respective hemisphere's dominance for these functions. However, considering the obvious asymmetries in bottom-up supply of cerebral blood — at the level of the large vessels arising from the aortic arch — it seems unwarranted to assume that asymmetric cerebral perfusion is purely a matter of top-down demand. Despite short-lived early theories of handedness-blood flow relationships in the 1860s, it is surprising that the geometric and hemodynamic asymmetries of the cerebral vascular system have never been comprehensively, accurately, and systematically investigated in relation to hemispheric lateralisation of function.

The present study hypothesises that hemispheric functional asymmetry is related to asymmetries in the vascular system. More specifically this study will investigate these asymmetries in the arterial geometry and hemodynamic properties of the branches of the aortic arch, including the brachiocephalic trunk (BT), left and right common carotid arteries (LCCA and RCCA respectively), left and right internal carotid arteries (LICA and RICA respectively) and left and right external carotid arteries (LECA and RECA respectively).

What is Handedness?

Handedness is the most obvious and best studied behavioural asymmetry in man (Cagnie et al., 2006). It refers to the preferential usage of one hand for unimanual tasks and/or the asymmetric proficiency in doing so (Corey et al., 2001; Papadatou-Pastou, 2011).

It is common practice in research to evaluate hand preference across a number of activities, placing it on a continuum ranging from extreme right-handed to extreme left-handed, with ambidextrousness in between (Rigal, 1992). Researchers who define handedness through the assessment of efficient task completion emphasise proficiency as the determining factor of hand dominance (Zillmer et al., 2008). Although a positive correlation has been demonstrated repeatedly between preference and proficiency, some studies reveal potential dissociation, suggesting that asymmetrical preference and proficiency may be distinct entities (Triggs et al., 2000).

It is important to keep in mind that lateralisation of function is multifaceted. Other behavioural examples include acoustic orientation, eyedness, and footedness asymmetries (Fitch, & Braccini, 2013). Nevertheless, handedness (in both senses of the word) is a common phenomenon, which assumes a J-shaped distribution, with preference for right hand use occurring in 85 to 95% of humans (Annett, 2002; Corballis, 2010). Between 6 and 16% of the world's population is left-handed, and 2 to 3% are ambidextrous, showing no clear hand preference or proficiency.

Handedness and Hemispheric Lateralisation

Right-handedness correlates strongly with asymmetries of cognitive, emotional, motor, and sensory processing (Hugdahl & Westerhausen, 2010). In right-handed individuals the left hemisphere almost always mediates praxic and language functions — with particular lateralisation to the left inferior frontal gyrus, as well as the left posterior temporal lobe of the brain (Broca's and Wernicke's areas respectively; Hopkins, 2013). Conversely, the right hemisphere is more involved in visuospatial and attentional functions in right-handers (Josse et al., 2004). This asymmetry is theorised to be a prerequisite for optimal function instead of an epiphenomenon of evolution or adaptation to the environment (Papadatou-Pastou, 2011).

The relationship between left-handedness and hemispheric specialisation is complex. Left-handed individuals are less laterally differentiated than right-handed individuals, as demonstrated by bilateral language functioning and transient aphasia following left hemisphere lesions (Hecaen & Sauguet, 1971; Knecht et al., 2000). The left-handed population is heterogeneous with respect to the direction of lateralisation, with approximately 60% reflecting right-handed lateralisation, whereas about 40% are bihemispheric or have a reverse pattern (Roberts, 1969).

The incidence of the right hemispheric language dominance increases linearly and significantly with the degree of left-handedness (Knecht et al. 2000).

Despite the multifaceted relationship between left-handedness and different aspects of hemispheric lateralisation, the strong association between right-handedness and left hemispheric specialisation for language and related cognitive and sensory-motor functioning has caused handedness to be widely employed as a reliable proxy for hemispheric specialisation in human neuropsychological research and clinical practice (Dadda et al., 2006).

Early Theories Regarding Handedness and Asymmetrical Blood Flow

The hypothesis that hemispheric lateralisation is related to asymmetrical blood flow and therefore to asymmetries in the cerebrovascular system, is not new (Cagnie et al., 2006; Zaina et al., 2003). In the middle to late 1800s, a number of theorists proposed that handedness was a product of various structural asymmetries of the body — including the asymmetrical arrangement of the internal organs of the body (“visceral” theory), increased arm length and bone weight of the dominant arm, and asymmetrical perfusion to the extremities (“subclavian artery” theory; Amunts et al., 2000; Buchanan, 1862). The “subclavian artery” theory postulated that handedness was as a direct result of higher perfusion to the right arm through the larger right subclavian artery (Hyrtl, 1860; Magendi, 1822). Despite evidence of this asymmetry, many scientists rejected the theory. Bichat (1805) considered the asymmetry insignificant, since the limbs themselves were symmetrical in volume and number of nerve fibres. A further ground for dismissal of the theory was that these asymmetries could not explain footedness (Bell, 1833).

Paul Broca’s (1827-1880) discovery of hemispheric lateralisation for speech in the 1860s caused a shift in the focus of the blood flow theory from the extremities to the brain. The “subclavian artery” theory was adapted to postulate the importance of blood flow asymmetry in cerebral lateralisation. The pioneers of this theory, Ogle (1871) and de Fleury (1873) argued that the dominant hemisphere received higher perfusion through the corresponding dominant ICA. Lueddeckens (1900) and Lombroso (1903) were also advocates of the theory.

It has long been known that the major arteries supplying the two cerebral hemispheres are asymmetrical. The right cerebral hemisphere is supplied from a vascular trunk which it shares with the right upper extremity, while the left hemisphere is supplied directly from the aortic arch (Figure 1.1; Alsaif & Ramadan, 2010). This asymmetry formed the basis of Ogle's early handedness-blood flow theory and predicted decreased flow efficiency in the arterial path feeding the right hemisphere, as additional branching results in blood flow disturbance, decreased vessel diameter, and increased vessel angle deviation (Ogle, 1871).

However, during his investigations of Ogle's theory, Broca (1877) concluded that despite the small influence the branching asymmetry may have on blood flow, this asymmetry has no decisive influence on the division of labour between the two cerebral hemispheres. He dismissed the theory on the basis that an inversion of the conventional vascular branching pattern (through *situs inversus totalis*) is not found in most left-handers. This dismissal was unfounded since carotid blood flow is influenced by multiple variables, and a reversal in branching is not necessarily the decisive factor in determining left-handedness.

Investigations of the handedness-blood flow theory have been sparse, flawed, relied on small samples, have presented a mixture of findings and have not always investigated the most appropriate arteries. With time the question of the role of blood flow in hand dominance and hemispheric lateralisation ceased to attract much attention and was seemingly forgotten. A systematic, large-scale, accurate, and comprehensive investigation into this question has yet to be conducted.

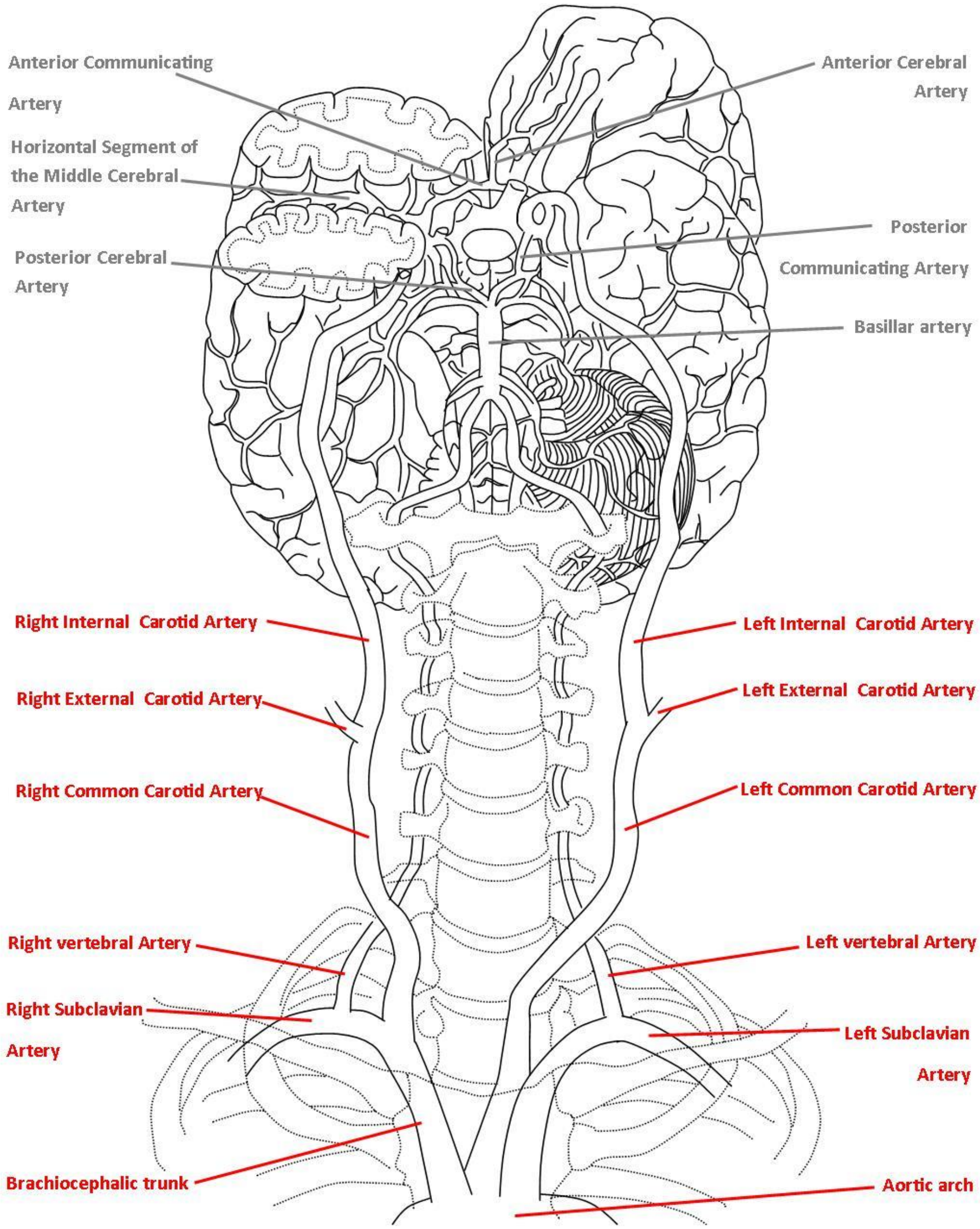

Figure 1.1. Major vasculature feeding the brain. A schematic drawing of the arteries superior to the aortic arch which regulate cerebral blood flow (with extracranial arteries indicated in red).

In order to systematically investigate the handedness-blood flow theory it is important to establish the extent of cerebral perfusion asymmetries at rest, during motor control as well as during cognition. Further understanding of the branching patterns of the aortic arch is required. There is need for a review of the literature that directly addresses the geometric and hemodynamic asymmetries of the ICAs, and CCAs, as well as the vertebral arteries. Due to the paucity of handedness measures in the majority of arterial studies, literature that indirectly suggests a handedness-related arterial asymmetry merits investigation.

Handedness and Asymmetrical Blood Flow

Asymmetries in cerebral blood flow. One of the largest arguments against the early handedness-blood flow theory was the discovery of the anterior communicating artery. As early as 1898 it was argued that the presence of the anterior communicating artery, which connects the two anterior cerebral arteries and forms part of the Circle of Willis, causes a pooling of the cerebral blood supply, and therefore equalises blood flow (and pressure) to both hemispheres (Kellogg, 1898).

However, the communicating arteries only become important to maintain sufficient brain perfusion in instances of arterial occlusion. Alastruey and colleagues (2007) found that flow of the anterior communicating artery in normal healthy subjects is small and only sufficient to keep the vessel active. In fact, anatomical variations with missing communicating arteries only alter the mean volume outflow rates in the middle and anterior cerebral arteries by less than 1% (Alastruey, Parker, Peiró, Byrd, & Sherwin, 2007). Therefore, since the middle and anterior cerebral arteries are overwhelmingly supplied by the ipsilateral ICA, the dismissal of the handedness-blood flow theory on this basis was unfounded.

Left-right lateral asymmetry is a normal attribute of cerebral perfusion, akin to asymmetries in brain morphology. Since over 80% of the blood delivery to the brain is achieved through the middle cerebral artery (Figure 1.2), most studies assess middle cerebral artery blood flow velocity to assess cerebral perfusion and lateralisation (Klingelhofer et al., 1997; Luczywek et al., 2003; Rihs et al., 1995; Stroobant & Vingerhoets, 2000). There is evidence of asymmetric cerebral perfusion at rest, during motor control, as well as during verbally mediated cognition.

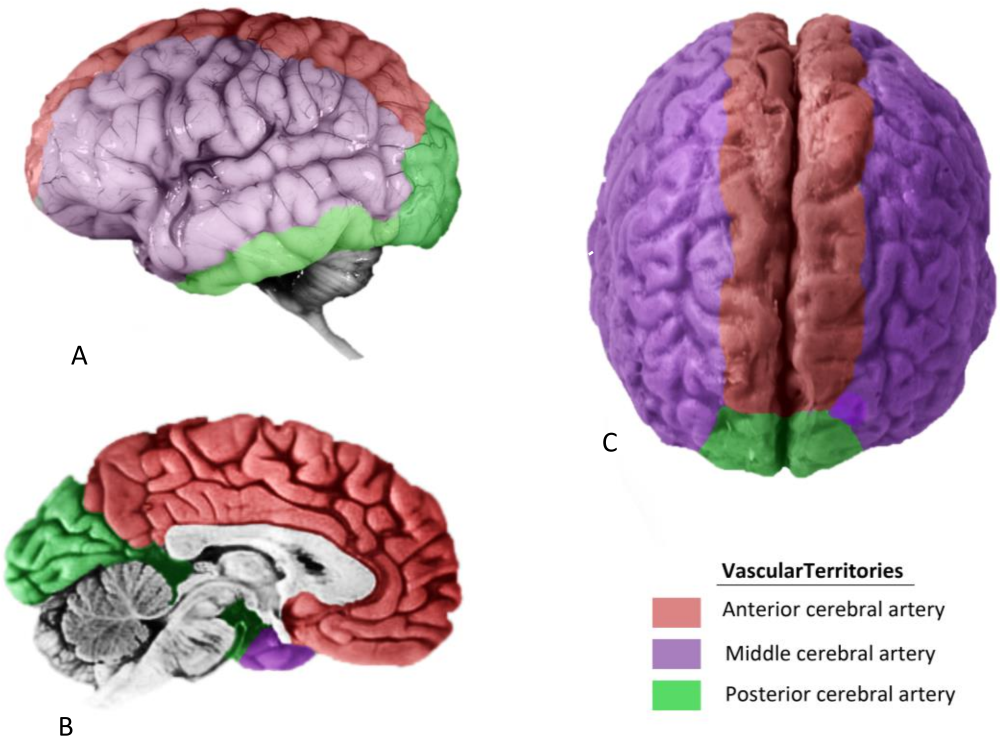

Figure 1.2. Cerebral perfusion territories. A schematic diagram of the three major cerebral territories on lateral (A), medial (B) and horizontal (C) views of the brain.

Asymmetries at rest. Functional hemispheric asymmetry is detectable in corticocortical connectivity and neuronal activity between the two hemispheres. In right-handed adults and school-age children, the left hemisphere typically reveals higher phase coherence and higher blood flow than the right (Gur et al., 1982; Thatcher et al., 1987).

Inconsistent findings have been reported for cerebral perfusion at rest (Haung & Seldic, 2013; Perlmutter et al., 1987). This can be attributed to varied methods, technologies and sample sizes, as well as the use of different definitions of the resting state. Nevertheless, studies have identified asymmetries of cerebral perfusion and metabolism between the hemispheres where metabolic activity favours the dominant hemisphere during sensory deprivation (Mazziotta & Phelps, 1984) and rest (Willis et al., 2002). Leutin and colleagues (2004) supported these findings by demonstrating higher maximum systolic velocity in the middle cerebral artery of the left hemisphere in right-handers, and higher linear blood velocity in the right hemisphere in left-handers. More specifically, higher cerebral blood flow is seen in the left prefrontal regions (Berman & Weinberger, 1990) and higher cerebral metabolic rates of oxygen in the left frontal and parieto-occipital cortex (Pantano et al., 1984). Many studies have also reported greater left than right perfusion in posterior cortical blood flow, including the precuneus (Pfefferbaum et al., 2010; Rodriguez et al., 1999). A territorial assessment of the three main cerebral arteries showed greater left than right perfusion of the anterior cerebral artery, the posterior branches of which supply the precuneus (Floyd et al., 2003; Figure 1.2). These studies all concern normal populations, in which right-handedness may be assumed for approximately 90% of participants.

Asymmetries during motor activity. Regional cerebral blood volume changes during motor activity (Matteis et al., 2001; Rijsberg & Ingvar, 1968). Studies show that activation of the contralateral primary motor cortex and dorsal premotor cortex is 20 times stronger than the activation of the ipsilateral cortex during complex distal hand movements (Haaland et al., 2004; Kim et al., 1993; Vivani et al., 1998). Right-handers with brain damage show greater ipsilateral motor impairment following left hemisphere damage versus right hemisphere damage (Haaland & Harrington, 1996). Handedness therefore reflects functional hemispheric asymmetry during motor control. The nature and extent of this asymmetry and its relation to hemispheric dominance have long been debated (Kim et al., 1993; Vivani et al., 1998). An extreme hypothesis argues that movement is initially generated in the dominant hemisphere and is subsequently replicated in the non-dominant one (Geschwind, 1975). This hypothesis is supported by studies of identical rhythmic movements, which illustrate that during the performance of motor tasks, the dominant hand leads the non-dominant one by approximately 25ms, irrespective of movement speed (Stucchi & Vivani, 1993).

Asymmetries during cognition. Cerebral blood flow changes during cognitive activity are highly dependent on the nature of the task. As expected, degree of handedness is highly correlated with middle cerebral artery blood velocity changes during verbally mediated cognition (Luczywek et al., 2003; Rihs et al., 1995). Language and mental arithmetic tasks result in a significant left-sided asymmetry in blood flow activation in the middle cerebral artery in right-handers (Bragoni et al., 2000; Bulla-Hellwig et al., 1996; Hartje et al., 1994; Szirmai et al., 2005; Thomas et al., 1995). Visuospatial tasks, on the other hand lead to a significant right-sided asymmetry in blood flow in the middle cerebral artery in right-handers (Bulla-Hellwig et al., 1996). Some left-handers have relative spatial bilaterality during mental rotation tasks (Shimoda et al., 2008). This is supported by lesion studies where spatial cognitive impairment in left-handers was caused by injury to either hemisphere, as opposed to the right hemisphere damage in right-handers (Hécaen et al., 1981). Nevertheless, Berman and Weinberger (1990) established that in right-handers prefrontal cortical activity in the dominant left hemisphere exceeds that of the right prefrontal cortex under most cognitive conditions.

Cerebral venous drainage. Left-right asymmetries in the venous drainage of the brain have been noted in the literature. An investigation into the relationship between cerebral lateralisation and the relative magnitude of the main superficial veins of the brain showed that participants with left-speech dominance (*n* = 34) had predominant veins of Labbé (closely situated to language-related regions) in the left hemisphere, and predominant veins of Trolard (covering the supero-parietal area) in the right hemisphere. However, participants with right-speech dominance (*n* = 9) showed the reverse pattern. Of these participants, only one showed an asymmetry where vein of Labbé was predominant on the left side (Di Chiro, 1962). These findings have been replicated in further studies (Di Chiro, 1972; Hochberg & LeMay, 1975). Importantly, the relationship between functional asymmetry and this morphological asymmetry is not yet clear (Herron, 2012).

Asymmetric arterial branching. As discussed, the vast majority of the population have a striking asymmetry in the origin of the carotid arteries — where the RCCA arises off of the BT and the LCCA arises directly off of the aorta (Figure 1.3). The geometry of this bifurcation is of substantial importance in determining the size of vortices and secondary flow regions in the vessel (Fisher & Fieman, 1990).

Variation in the anatomy of the aortic arch and its branches in humans are mostly asymptomatic. The most common branch variant, the “bovine arch” — occurring in approximately 20% of the population — maintains the branching asymmetry of conventional branching patterns with the added characteristic of a common origin between the LCCA and BT (Figure 1.3; Alsaif & Ramadan, 2010; Gupta & Sodhi, 2005). Other less common variations occur, where an aberrant right subclavian artery or left vertebral artery arises directly out of the aortic arch (Figure 1.3; Jakanani & Adair, 2010; Kanne & Godwin, 2010). Abnormal branching patterns at the level of the aortic arch may cause the subsequent vessels to contribute to cerebral blood flow in varying ways. It is imperative to investigate branching patterns and their unique geometrical characteristics when assessing asymmetrical blood flow. Surprisingly, this has never been done.

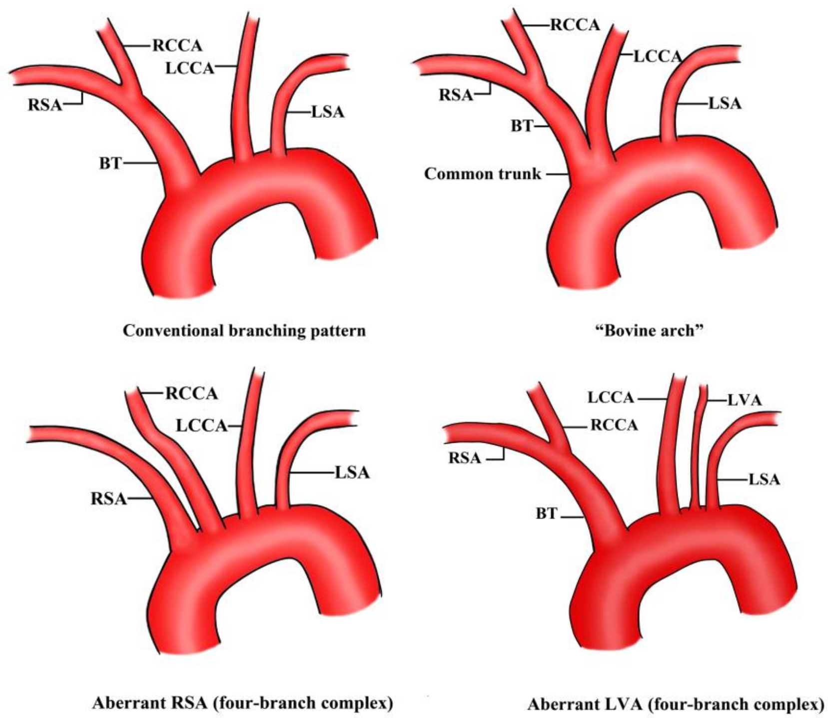

Figure 1.3. Common variations of aortic arch branching patterns. Schematic drawings of three major aortic branching variations found in humans. RSA= right subclavian artery; LSA= left subclavian artery, LVA = left vertebral artery.

Interestingly, in most mammals the vasculature feeding the hemispheres branch symmetrically from the brachiocephalic trunk (Figure 1.4; Carmon & Gamos, 1970; Shepherd, 1884). This is not surprising since there is no evidence for a population-wide lateral preference similar to that of humans in other species ― which is only said to occur when more than 50% of the members of a population are lateralised in the same direction[1] (Bisazza et al., 1998; Carmon

[1] The strongest claims for non-human handedness come from work with primates in captive settings (Marchant & McGrew, 2013). The laterality in captive primates may be attributed to the experiences of the apes being raised in a right-handed human environment. This is not surprising since culture and context readily influences the expression and extent of handedness in all human societies (Faurie, 2005). However, studies of laterality in primates that measure multiple naturalised behaviours in non-captive settings find hand preference equally distributed in the population, and therefore fail to identify population trends towards right or left-handedness (Corp & Byrne, 2004; Llorente et al., 2011; McGrew & Marchant, 2001).

et al., 1972; Hopkins, 2013; Marchant & McGrew, 2013; Martin & Jones, 1999). Exceptions to the symmetrical origin of the carotid arteries in mammals are rare and are only significantly observed in anthropoid monkeys, gorilla and chimpanzees (Osman-Hill, 1953). It would be important to determine the extent to which these exceptions correlate with or show tendencies toward population-wide handedness.

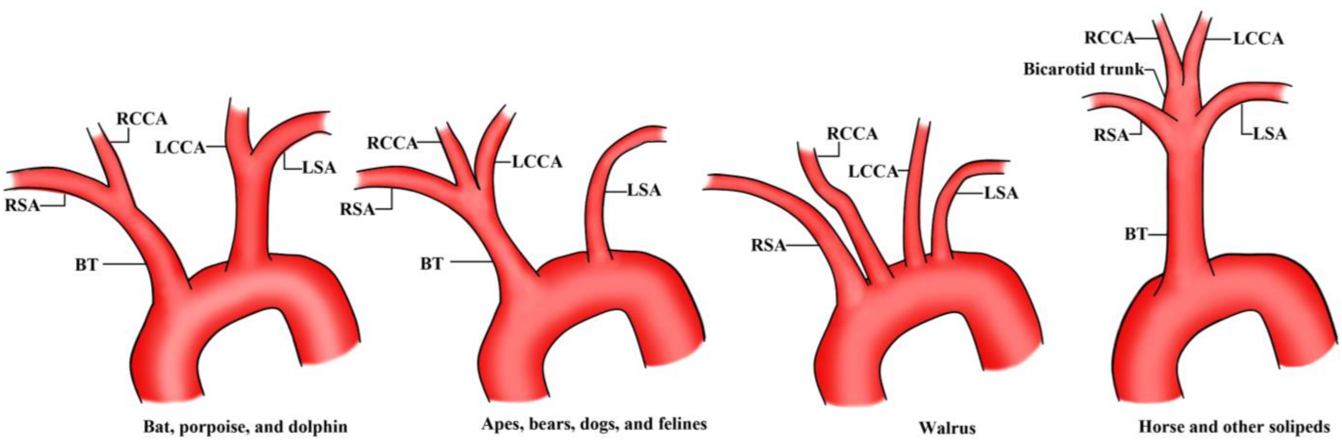

Figure 1.4. Schematic drawings of four major symmetric aortic branching variations found in other mammals. RSA= right subclavian artery; LSA= left subclavian artery.

Asymmetries in arterial blood flow. Arteriographic studies conclude that the mechanical properties of large arteries play an important role in regulation of cerebral blood flow (Magun, 1973; Nichols & O'Rourke, 1998). Arteries resist blood flow based on their geometric features. This forms an important pressure gradient across the arteries between the aorta and the large arteries of the brain (Kanzow & Dieckhoff, 1969). Luminal diameter is the most influential geometric property related to blood flow resistance, which in turn has physiological implications as illustrated in Figure 1.5 (Ku, 1997; Lusis, 2000; Mitchell, 2003; 2004). Side branches and mild curvatures as low as 15^{o} are sufficient to influence blood flow (Banerjee et al., 1992; Manbachi et al., 2011; Staalsen et al., 1995). More specifically, curvatures result in swirling, flow separation, and secondary flow — which are most influential when the flow decelerates (Doorly & Sherwin, 2009; Ku, 1997; Leguy et al., 2009). Ogle (1871) argued that degree of vessel curvature, distance to bifurcation, as well as relative differences in vessel calibre and length will vary the degree of advantage enjoyed by the left hemisphere and thus also account for variations in the degree of handedness.

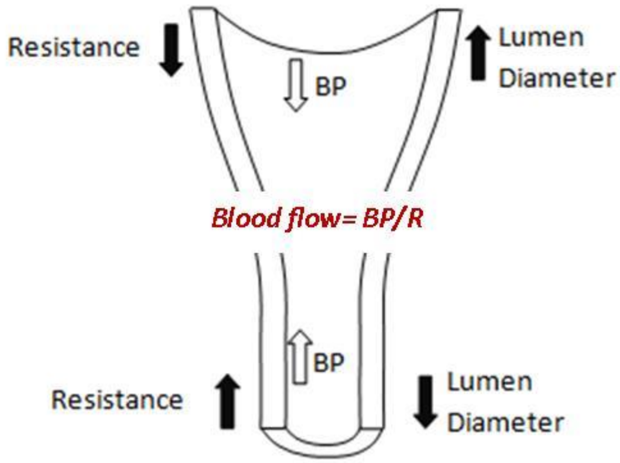

Figure 1.5. Hemodynamic principles of arterial blood flow. A schematic diagram illustrating the interactions between BP (blood pressure), lumen diameter, and vessel resistance

Despite the importance of the properties of the larger arteries for cerebral blood flow, most geometric and hemodynamic studies of the branches of the aortic arch do not explicitly investigate handedness relationships. This leaves the possibility that asymmetries in arterial blood flow at the 'supply' level might underpin cerebral lateralisation, essentially uninvestigated. Nevertheless, strong arguments for significant handedness-related arterial asymmetries can be made.

Vertebral arteries. Many post mortem angiographic and sonographic studies note that the left vertebral artery is typically larger than the right (Abd-el Bary et al., 1995; Mitchell, 2004; Scialfa et al., 1975; Seidel et al., 1999; Thiel et al., 1994; Yuan et al., 1994). However, despite differences in diameter, flow velocities, and blood flow volumes, these asymmetries do not correlate with handedness (Cagnie et al., 2006; Jeng & Yip, 2004). This is not surprising considering that the vertebral arteries merge in the basilar artery before they supply the cerebrum via the posterior cerebral arteries (Figure 1.1).

Internal carotid arteries. The CCAs supply the bulk of the cerebrum via the ICAs, which bifurcate to form the middle and anterior cerebral arteries and therefore directly contribute to cerebral blood flow (Figure 1.1 and 1.2). The nature of this contribution is supported by perfusion imaging studies which quantify regional cerebral perfusion in the ICA territory (see Lee et al., 2004 for perfusion probabilistic maps). In fact, hemispheric cerebral blood flow values show a close and linear correlation with blood flow volumes of the ICAs, $r = 0.76$; $p < 0.001$ (Soustiel et al., 2003).

Not only do the ICAs supply blood to substantial parts of the brain, these vessels are most frequently involved in vascular pathology (Johansson et al., 2000; Mead et al., 1998). Consequently, branching and geometric asymmetries in these arteries should be key to exploring asymmetrical cerebral blood flow (Mitchell, 2004).

There is little literature regarding the relation between the hemodynamic and geometric asymmetries of the right and left ICAs and handedness. An early attempt by Ogle (1871), autopsied 17 right-handed and 3 left-handed males. In 12 out of 17 right-handers, either the CCA or the ICA was larger on the left. Conversely, in one of the three left-handers, the RCCA and RICA were both nearly twice the size of the corresponding vessels on the left. The left-handers further demonstrated a similar disproportion in the middle cerebral vessels, which were also in favour of the right.

Two studies are often identified to have discredited Ogle's early vascularisation theory — both of which claim no consistent size differences between the left and right ICAs. However, these studies are highly flawed and therefore have little scientific credibility. In his early study of 24 cranial specimens, Cunningham (1902) concluded that considerable size differences between ICAs often favoured the left or right — making the overall difference negligible. Cunningham (1902) selected the small sample of 24 skulls at random, and therefore had no indication of each specimen's handedness. Furthermore, measurements consisted of printings of wax moulds of the carotid canal, through which the ICA enters the cranium. ICA cross sectional area was therefore not directly measured, but rather inferred from the cranial cavities.

Crichton-Browne, (1907) reported negligible side-to-side differences between the ICAs based on diameter measures of ring cuttings taken of the LICA and RICA (2.75mm and 2.8mm respectively in men, and 2.6mm in both arteries in women). However, handedness was not measured in Crichton-Browne's small samples of only 10 male and 10 female participants. Little is documented regarding the methodology used in the carotid measures. However, it is clear that the cuttings only involved single, once-off measurements of the arteries in an unspecified location within the cranium. This is not an accurate reflection of the three-dimensional geometry of the carotids.

More recent studies present a mixture of findings regarding LICA and RICA asymmetries. An ophthalmodynamometry study involving 110 young healthy subjects found that the systolic (and to a lesser degree, the diastolic) ophthalmic artery pressures are higher on the right side of right-handed subjects, higher on the left side of left-handed subjects, and equal in both sides of most ambidextrous subjects (Carmon & Gamos, 1970). These ophthalmic artery pressure differences reflect pressure differences in the right and left ICAs. This increased pressure in the right blood vessels of right-handers might be explained by significantly smaller diameters of the RICA as well as its terminal branches, as compared to the left. Because cerebral metabolic conditions are more favourable on the side where the pressure is lower, due to a lengthening of the effective systole time in the respective hemisphere, this hemodynamic asymmetry reflects a handedness-related bias (Carmon & Gamos, 1970).

Bogren et al. (1994) established normal carotid artery flow rates in five left-handed and five right-handed individuals. Right-handers had higher flow rates in the LICA than in the RICA, and the opposite was true for the left-handers (p = .007).

Despite not assessing handedness, Müller et al. (1991) reported the diameters of bilateral ICAs, anterior and middle cerebral arteries, measured by angiography. They demonstrated that in participants aged 11 to 20 years, the diameters of ICAs and anterior cerebral arteries were significantly larger on the left compared to the right.

However, other studies (with no handedness components) found little difference between left and right CCAs and ICAs (Limbu et al., 2006; Scheel, Ruge, & Schöning, 2000).

Common carotid arteries. Because the ICAs branch from larger vessels which originate at or very close to the aortic arch, cerebral blood flow is directly influenced by the characteristics of these large calibre vessels. There is very little research regarding CCA asymmetries. An early geometric study by Bennecke (1878) found the average RCCA to be larger in most age groups of 485 post mortem cases. However, his study did not assess handedness, other geometric variables, or investigate minimum lumen diameter — which would have the most influence on carotid blood flow. Furthermore, Uematsu et al. (1983) demonstrated that the LCCA wall motion is consistently larger than the RCCA wall motion in 120 normal control subjects.

Many studies describe higher peak systolic and mean velocities in the LCCA than in the RCCA (Donis et al., 1988; Luo, Yang, Cao, & Li, 2011; Schöning, Walter & Scheel, 1994; Zbornikova & Lassvik, 1986). Although Bogren et al. (1994) established handedness-blood flow asymmetries in the ICAs (as previously mentioned), the same study failed to demonstrate these flow asymmetries in the CCAs, possibly due to their small sample size (N = 10). However, significant differences in blood flow waveforms have been noted between the two CCAs in an analysis of 3560 cardiac cycles (Holdsworth et al., 1999). Timing parameters of the blood waveform in the LCCA lead the RCCA waveform by 2.3ms (Holdsworth et al., 1999). These timing parameters were significantly different for T_{MIN}[2], T_{A_MAX}[3], and T_{DN}[4]. Furthermore maximum systolic velocity parameters also exhibited a contralateral bias, with the left side exceeding the right by 4.9cm.s^{-1}.

Studies of intima-media wall thickness, as measured by B-mode ultrasonography, have reported significant differences between left and right CCAs in right-handed individuals — where intima-media wall thickness is typically higher on the left side (Denarie et al., 2000; Lemme et al., 1995; Oxenham & Sharpe, 2003; Rodriguez-Hernandez et al., 2003; Simon et al., 2002). This is presumably because the hemodynamic stress and intimal damage, and therefore shear stress and wall tension, is larger in the LCCA in right-handed versus left-handed individuals (Carallo et al., 1999; Önbaş et al., 2007; Shaaban & Duerinckx, 2000). This thickening therefore provides indirect evidence of asymmetry of blood flow.

Vascular Pathology

The carotid arteries are of special interest to many researchers because of the clinical importance of their complex flow properties and preferential development of atherosclerosis (Manbachi et al., 2011). These studies pay particular attention to the site of bifurcation of the CCAs into the ICAs and ECAs — which is characterised by turbulent flow and increased wall shear stress (Malek et al., 1999). Research indicates that as many as 30% of all major hemispheric events originate from disease at the carotid bifurcation (Timsit et al., 1992).

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[2] Time of diastolic minimum velocity
[3] Time of maximum acceleration
[4] Minimum velocity in dicrotic notch

It has been suggested that a predilection for cerebrovascular disease exists on the left side — as shown by the higher incidence of left versus right nonlacunar cerebrovascular strokes (Rodriguez-Hernandez et al., 2003). These findings are related to greater hemodynamic stress and intimal damage in the LCCA in right-handed individuals.

Situs inversus. The idea that *situs inversus totalis* was responsible for left-handedness belongs to Ludovico Ricchieri (1450-1520). However, this theory was quickly discredited for statistical reasons (Browne, 1646).

Classic studies of handedness in *situs inversus totalis* failed to assess carotid geometry or undertake blood flow analyses (Cockayne, 1938; Gordon, 1998; Torgersen, 1950; Watson, 1936). Most *situs inversus totalis* individuals are not left-handed (Afzelius, & Sternam, 2006). This might appear to be strong evidence against the hypothesis that 'supply' side asymmetry underpins cerebral lateralisation. However, mirror reversal of the aortic arch would not necessarily result in a reversal of CCA origins and geometries, and therefore blood flow differences. These questions have simply never been investigated. It is possible that arteries follow the intended genetic laterality pattern during periods of rapid arterial growth in infancy, despite the aortic reversal. Further research is required to determine blood flow patterns in this rare anatomical anomaly.

Evidence toward a Causal Relationship

Importantly, direction of causality cannot be determined from any of the studies reviewed above. It remains possible that all the asymmetries observed (apart from the typical aortic branching pattern in humans, Figure 1.3) are effects rather than causes of cerebral lateralisation. However, recent developmental studies provide compelling information regarding the likely directionality.

The developing brain shows marked asymmetries by the second trimester of pregnancy. The cortical fissures, folds around the sylvian area, as well as high-order dendritic branches consistently appear earlier in the right hemisphere (De Schonen & Deruelle, 1991; Dooling et al., 1983; Chi et al., 1977; Nowakowski, 1987; Simonds & Scheibel, 1989). Furthermore, areas of the right hemisphere mature more quickly than homologous areas in the left hemisphere, such as the areas responsible for facial recognition (De Schonen & Mathivet, 1989; Hellige, 1993; Turkewitz, 1988).

During the development of functional brain asymmetry, a marked shift occurs in cerebral blood perfusion. While blood flow shows superior perfusion of the right hemisphere between one and three years of age, this asymmetry shifts to the left after three years (Chiron et al., 1997). The right-to-left sequence of asymmetry seems to be related to the consecutive emergence of functions dedicated to the right (visuospatial abilities), and then to the left hemisphere (language abilities). For instance, the left regional cerebral blood flow predominance in the sensorimotor region that emerges at approximately two and a half years of age coincides with the usual development of right-handedness and fine motor skills at this age (Chiron et al., 1997).

Anatomical arterial developmental studies also reveal a shift in carotid arterial development, *before* age three. More specifically, the change in carotid arterial diameter with pulse pressure increases gradually until two to three years of age (Kojo et al., 1998). Similarly, on a hemodynamic level, mean, maximum and minimum carotid arterial blood flow increases steadily and significantly in infants older than one month, and reach a plateau between two to four years of age. This indicates that carotid arterial diameter and subsequent blood flow changes with age in the first three years of life, reflecting a change in cardiac contraction and the carotid cerebral circulatory system (Kojo et al., 1996) which gradually favours the perfusion of the left cerebral hemisphere.

It seems, therefore, that the anatomical and hemodynamic characteristics of the left and right CCAs may precede the functional establishment of hemispheric dominance around the age of three. If this is the case, a causal relationship could be established. However, this question needs to be investigated directly.

Study of bilateral carotid diameters in children are limited — as most pediatric studies only measure one of the carotids (usually right) or average parameters of the left and right carotids together. Bode and Wais (1988) report intra-individual variation of flow velocities between 2% and 8% in their bilateral examination of ICAs in newborns. However, the extent and direction of this variability is not specified, although some studies argue that no significant side-to-side differences in carotid waveforms (Gray, Griffin, Drumm, Fitzgerald & Duignan, 1983) and diameter (Uematsu, et al., 1983) exist in neonates.

Summary and Conclusions

Despite the vast history of handedness research in the fields of anthropology, genetics, neuroscience, paleoanthropology, psychology and psychiatry, the determinants of human handedness, and therefore for neurocognitive asymmetry, remain unknown (Amunts, et al., 2000; McGrew, Marchant & Schiefenhövel, 2013; Vuoksimaa et al., 2009). Nevertheless, it is clear that the geometric parameters of the carotid arteries vary considerably and correspond with handedness. Most evidence for this relationship is indirect and therefore is representative of asymmetries in right-handed individuals. Comprehensive, large scale, valid investigations into the relationship between the geometric and hemodynamic asymmetries of the primary aortic branches and hand dominance (as a measure of cerebral asymmetry) need to be conducted. Complex interactions of hemodynamic principles require an in-depth anatomical and hemodynamic investigation.

Overall Aim and Hypothesis

The following general hypothesis was examined in the two ensuing chapters:

H_1: In individuals with conventional aortic branching patterning, the geometric and hemodynamic characteristics of the left and right extracranial arterial branches facilitate increased blood supply in the cerebral arteries contralateral to the dominant hand.

Chapter 2: Geometric Characterisation

The carotid artery bifurcation has been the subject of intensive anatomical and hemodynamic study owing to the preferential development of atherosclerosis at this site (Manbachi et al., 2011). Less well studied are the anatomy and hemodynamics of the CCAs. Nevertheless, it is clear that the geometric parameters of the carotid arteries vary considerably and contribute to a corresponding variability in its local hemodynamics (Affeld, Goubergrits, Fernandez-Britto, & Falcon, 1998).

Considering the extent to which a small variation in geometry can influence and completely change flow patterns, geometric analyses of the carotid arteries are essential to identify potential left-right handedness related asymmetries (Affeld et al., 1998; Holdsworth et al., 1999).

Pilot Study

The 2012 pilot study of 71 participants (8 left-handed; 62 right-handed; 1 ambidextrous) aged 21 to 96 years (M = 57.32 years) provided compelling evidence that the geometric characteristics of the LCCA and combined RCCA and BT (RCCA-BT complex) are asymmetrical, in a direction that promotes blood supply to the respective dominant hemispheres in right-handed and left-handed individuals. In particular, these asymmetries were found in arterial length, minimum diameter, and calculated resistance to blood flow. These variables showed particularly high effect sizes, thereby validating the practical significance of the findings. However, replication using a larger number of left-handed participants was needed to increase the statistical validity of these findings. Furthermore, the complex hemodynamic relationship between arterial resistance and blood flow required the measurement of hemodynamic parameters to improve the validity of the asymmetry. These limitations were addressed in the current study.

Specific Aims and Hypotheses

The following sub-hypothesis was examined:

H_1: In individuals with a conventional aortic branching pattern, the geometric characteristics of the LCCA and the RCCA-BT complex facilitate increased blood flow in the artery contralateral to the dominant hand.

The following questions were addressed:

1. Are there significant geometric differences between the LCCA and the RCCA-BT complex in left-handed versus right-handed individuals?
2. Is there a relationship between these characteristics of the LCCA and the RCCA-BT complex and handedness?
3. Can these variables predict handedness?
4. How do these variables change with age?
5. How do unconventional branching patterns influence these characteristics and this potential relationship?

Design and Methods

Design and Setting

This study aimed to investigate the structural asymmetry of the extracranial arteries supplying the cerebral hemispheres and its relation to handedness. A non-experimental quantitative design was utilised, allowing for analysis of numerical data. This involved the measurement of potential relationships between handedness and multiple geometric asymmetries of the LCCA and the RCCA-BT complex. The geometric variables in question were selected based on the strong theoretical basis for their direct influence on arterial blood flow.

Participants

The study involved an initial sample of 1060 participants. Extensive exclusion criteria were adopted to ensure that the results were not confounded by extraneous variables (see below). Consequently, existing CTA scans of 199 radiology patients were included in the study from five hospitals located in Cape Town, Centurion, and Pretoria, South Africa. All CTA scans were administered between 2009 and 2014 — this ensured the use of recent data, collected with the same modern technologies and procedures, and increased the likelihood that participants were available for contact. A non-randomised participant sampling approach was used. A total of 174 right-handed, 23 left-handed, and 4 ambidextrous participants (129 male; 71 female) ranging between 15 and 92 years of age (*M* = 52 years) were included in the study (Table 2.1). The wide age range controlled for the influence of empirically established age related changes in the structure and function of the cardiovascular system such as progressive dilatation and elongation of major arteries, increased tortuosity, and arterial stiffness (Oxenham & Sharpe, 2003).

Participants were divided into the handedness categories based on a laterality quotient (LQ) which was generated by a revised version of the Edinburgh Handedness Inventory. Participants with a LQ ≥ 30 were classified right-handed. Those with a LQ ≤ 20 were classified left-handed, and those with a LQ between 21 and 29 were classified ambidextrous. This ratio is also used in the original Edinburgh Handedness Inventory.

Patients with congenital anomalies of unconventional aortic arch branching patterns were analysed separately to investigate further geometrical abnormalities (providing additional insights into the nature of the relationship between asymmetrical arteries and handedness).

Exclusion criteria. Deceased participants, as well as those who provided inaccurate or outdated contact information, and could not be contacted to ascertain their handedness were excluded from the study. Patients diagnosed with pathological vascular abnormalities of the LCCA, BT and/or RCCA (including atherosclerotic disease, arterial stenosis, aneurysm, arterial dissections and other traumatic vascular injuries) were excluded. Any CTA that was incomplete, wrongly formatted, or unclear, was also removed. Two participants reported social pressure to change their handedness and were removed from the study.

Table 2.1

Descriptive statistics for participants as a function of handedness.

		Right-handed	Left-handed	Ambidextrous	Total
N		172	23	4	**199**
Sex (%)	Male	63.79	73.91	25	**63.81**
	Female	35.04	26.09	60	**35.67**
Age (SD)		51.73 (18.79)	52.96 (18.20)	62.5 (11.39)	**52.10 (18.61)**
Branching Pattern (%)	Conventional	78.49	82.61	100	79.40
	"Bovine arch"	16.28	17.39	-	16.08
	Aberrant RSA	1.16	-	-	1.01
	Aberrant LVA	2.32	17.39	-	2.01
	Other	1.16	-	-	1.01

Note. RSA = right subclavian artery; LVA = left vertebral artery.

Materials

Revised Edinburgh Handedness Inventory. Handedness was assessed telephonically via the administration of a revised version of the Edinburgh Handedness Inventory (Appendix A and B), one of the most popular pencil and paper tests developed for hand preference classification (White & Ashton, 1975). Scores obtained from this inventory formed a participant LQ, which ranged from 0 (all left) to 50 (all right) (Oldfield, 1975). This version of the inventory did not provide the option of placing a double score for extreme handedness and did not allow indifferent subjects to place a score in both the right and the left columns (Oldfield, 1975). These adaptations addressed common scoring criticisms of the traditional Edinburgh Handedness Inventory (Oldfield, 1975; Williams, 1991).

CTA Scanning. CTA scans were performed using 64 Detector/Slice Toshiba Multidetector CT scanners at each of the respective hospitals.

Imaging software. Radiant DICOM Viewer (64-bit) imaging software was used for the geometric analysis of the arteries.

Procedure

Administration of Handedness Inventory. Interviews were conducted by the author — who remained blind to the nature of the respective CTA scans. Once informed consent or assent was obtained, the inventory was administered. Each interview lasted approximately 7 minutes and was conducted in English (Appendix A) or Afrikaans (Appendix B), depending on the language preference of the participant. Each interview followed the same procedure. Scores were recorded, an LQ was calculated, and participants were grouped accordingly. Participants were also asked whether they were pressured into changing their handedness at a young age.

CTA Scanning. Standard medical procedures were followed during CTA scanning — taking approximately 10 seconds each. All source data was stored on a server at the respective hospitals, from which it was accessed via a picture archive and imaging system.

Image processing and vessel analysis. The source CTA data for the participants were imported into a workstation running the Vitrea Core software V.6.2.1 (Vital Images). Using the software's vascular package, a three-dimensional model of the cerebral vasculature with automated removal of the bone and soft tissues was generated. This data were then imported into Radiant DICOM Viewer (64-bit) imaging software, where geometric analyses of the relevant arteries were performed — the author remained blind to the identity and LQ of each participant throughout these analyses. Each analysis took approximately 45 minutes to one hour to complete.

Length. The proximal and distal ends of the vessels under evaluation were manually selected — within 3 mm of the vessel origin and terminus. The length of the LCCA and the full length of the RCCA-BT complex, between the proximal and distal ends were measured (performed in the coronal and sagittal planes). The longest of these measurements for the two arteries was recorded to ensure that the true length of each vessel was documented to control for angle deviations of the vessel (Kanitsar, Wegenkittl, Fleischmann, & Groller, 2006). BT lengths were also measured separately and recorded.

Diameter and area. Vessel diameters (mm) and areas (mm^2) of these vessels were determined at five regular intervals — namely at the (1) distal end, (2) 25th percentile, (3) 50th percentile, (4) 75th percentile, and (5) the proximal end of the vessels. The longest and the shortest lumen diameters in the axial plane were measured manually and the means recorded to ensure control for the shape of the vessel lumen. Area was recorded with the specialised tool of the Radiant DICOM Viewer at each of the intervals. Maximum (D_{MAX}) and minimum (D_{MIN})

diameters, and areas of these measurements, were selected for further analysis. Mean diameters were excluded from the results as they are skewed by the larger diameter of the BT.

Angle. Two categories of vessel angles were measured.

Firstly, the extent to which the vessels deviate from the vertical (the most direct path to the brain) was measured. This was done by constructing a vertical line in the Radiant DICOM Viewer and measuring each instance of angle deviation from this vertical line (in the coronal and sagittal planes), including the angle to which the arteries bifurcated off the aortic arch. Deviations of less than 5° were excluded, as this deviation has negligible effects on blood flow (Staalsen et al., 1995). Total accumulative angle deviation (DEV_{SUM}) and mean angle deviation (DEV_{MEAN}) of the two vessels were recorded to ensure that the true three-dimensional deviation of each vessel was documented.

Secondly, the arterial curvatures were directly measured. This included the calculation of the mean artery angles (A_{MEAN}) of the vessels. Centre lines were constructed along the longitudinal axis of the blood vessels at each instance of curvature. The angle of this curvature was measured in the coronal and sagittal planes. This was done throughout the length of the vessels and included the curvature of the straightest component of each vessel. Mean values for the LCCA and the RCCA-BT complex were calculated. Given the nature of this measurement, the closer the mean vessel angle was to 180°, the straighter it was. Total accumulative arterial angles (A_{SUM}) of each artery were also recorded.

Resistance to blood flow. In order to account for the strong influence of diameter on resistance to blood flow (to the forth power), Poiseuille's formula was used to calculate the overall resistance of the two vessels of interest:

$$Rx = \frac{8.\eta.L}{\pi.r^4}$$

where η = blood viscosity; L = vessel length; π = the mathematical constant Pi; and r = lumen radius (Iordache & Remuzzi, 1995). The equation assumes that the fluid is incompressible and Newtonian with laminar flow. Although blood can exhibit non-Newtonian behaviour (such as shear thinning and viscoelasticity), the Newtonian assumption is considered acceptable as an approximation for the flow in medium-to-large vessels (Nichols & O'Rourke, 1997; Pedley, 1980; Quarteroni, Tuveri, & Veneziani, 2000). Although this model applies to non-curved vessels, the carotid arteries are considered straight enough to justify the assumption of fully developed blood flow in Poiseuille's formula (Iordache & Remuzzi, 1995). Despite some dispute regarding the accuracy of this calculation, systemic vascular resistance remains the most usable approximation of the total opposition to flow (Wigfull & Cohen, 2005). No data was available concerning the blood viscosity (η) of the participants, so a normative viscosity 3.5×10^{-3} Pa.s at 37°C was assumed (Rosenson, McCormick, & Uretz, 1996) as there is no reason to suspect that blood viscosity differs between left-handed and right-handed individuals.

Statistical Analysis

Data was analysed using the IBM SPSS Statistics (version 22) software. Frequency tables and box-and-whisker plots were created in order to better understand the distribution of the data (William, 1980).

One-tailed paired t-tests were used to compare the differences between the left and right arterial geometric parameters of the handedness groups, as classified by their LQ. Normality tests, namely the Shapiro-Wilk, Kolmogrov-Smirnov, and Lillifors were run on each data set. If the assumption of normality was not upheld, a non-parametric Wilcoxon signed-rank test was run instead. Sample specific descriptive statistics of age, sex, and handedness were also included.

The main data analysis consisted of a series of mixed-design ANOVAs in order to assess interactions between arterial geometry and handedness. For each analysis, the within-subjects factor was the respective arterial geometric parameter (of the left and right CCAs) and the between-subjects factor was the participant's handedness (left-handed, right-handed, and ambidextrous). All analyses were conducted on participants with conventional aortic branching patterning. Tests of homoscedasticity (namely Levene's test of equality of variance and Box's test of equality of covariance matrices) were run on each dataset and were upheld. Evidence suggests that *F* controls the Type I error rate well under conditions of skew, kurtosis and non-normality (Glass, Peckham, & Sanders, 1972). Consequently, all assumptions of the mixed-design ANOVA were upheld. Pairwise Bonferroni post-hoc tests were run to identify significant differences within each significant handedness interaction effect.

A discriminant function analysis was used to determine the predictability of handedness based on arterial resistance to blood flow. Significant predictor variables of handedness were therefore statistically identified (Cooley & Lohnes, 1971). The independent variables of this analysis were the geometric predictors and the dependent variables were the handedness groups, as determined by the participants LQ. Prior to analysis, the predictor variables were inspected to ensure that the assumptions for the analysis were upheld (Klecka, 1980). Since the DFA is considered fairly robust to violations of normality, all assumptions were upheld (Klecka, 1980).

The following predictor variables were used in the analysis: X1= LCCA resistance, X2= RCCA-BT complex resistance. The significance of the discriminant function analysis was determined by an *F*-test, with a 95% confidence level, $p < .05$. Ambidextrous participants were removed from the analysis due to the small sample size ($n = 4$).

Simple linear regressions were run to investigate the age-related changes in arterial geometry in left-and right-handers. Bivariate correlation matrices (Pearson's and Spearman's) illustrated the relationship between each geometric predictor variable and age. Scatterplots were used to visually illustrate the trends in the data. Due to the high correlation between DEV_{MEAN} and DEV_{SUM} (RCCA-BT $r(158) = .896$, $p < .001$; LCCA $r(158) = .909$, $p < .001$) and between A_{MEAN} and A_{SUM} (RCCA-BT $r(158) = .929$, $p < .001$; LCCA $r(158) = .921$, $p < .001$), only summative angle measures of each artery were included in the analysis. All assumptions of the regression analyses were upheld.

Cohen’s (1992) rule of thumb for effect size interpretations were used for within-group and between-group comparisons: $d = .10$ (small effect), $d = .30$ (medium effect), and $d = .50$ (large effect). Results of all analyses were considered significant when the p value was less than .05.

Cases of unconventional branching patterns were removed from the main analysis. Two-tailed independent t-tests were used to compare the geometry of unconventional branching patterns to conventional branching patterned participants. Two-tailed paired t-tests were used to compare the differences between the left and right arterial geometric parameters within the “bovine arch” branching group to detect significant side-to-side asymmetries.

Ethical Considerations

The study followed the guidelines for research with human subjects as outlined by the University of Cape Town as well as ethical standards as stipulated by the Health Professions Council of South Africa, and the latest version of the Declaration of Helsinki. Ethical approval from the University of Cape Town Psychology Department as well as from the University of Cape Town’s Faculty of Health Science Research Ethics Committees was obtained. Ethical approval was granted by all hospitals included in the study. Informed consent was obtained from each participant before the CTAs were released into the custody of the primary investigator (Appendix D and E). Consent was obtained in English or Afrikaans (depending on language preference). However, if the participant was incapable of conversing in these languages, they were excluded from the study. Parental assent was obtained for paediatric cases in this study (Appendix D and E).

Information obtained from the analysis was used solely for the study, and was kept confidential. The participants were informed of the purpose of the research, and assured that their involvement was voluntary and that they could withdraw from the study at any stage without negative repercussions. In the event that a participant withdrew from the study, the CTA was deleted and all related information was removed.

Nothing was required from participants other than disclosing their handedness. No medical, personal, or intimate information was disclosed to the primary investigator. Only name, telephone number (both of which were used to get consent and deleted once consent was obtained), sex, and age at which the scan was administered was disclosed.

Participants were informed that in the event of the discovery of a previously undetected anatomical abnormality during the CTA analysis, confidentiality may be broken, and the relevant hospital would contact the participant, and discuss medical management. Debriefing was offered to all participants. There were no overt risks or immediate benefits to the participants.

Results

Results for Chapter 2 are presented in four sections. The first section involves the direct analysis of handedness-related geometric asymmetries of participants with (i) conventional branching patterns — including arterial lengths, diameters, curvatures and resistance to blood flow. For brevity, area measures for each artery were omitted from the tables, as they reflected diameter findings. This section is followed by (ii) a discriminant function analysis assessing the accuracy to which handedness can be classified according to arterial resistance, and (iii) simple linear regression analyses investigating the extent to which arterial geometry changes with increasing age in left-and right-handed groups. The last section investigates arterial asymmetries in (iv) cases of unconventional branching.

Of the 199 participants, 172 were right-handed (86.43%), 23 were left-handed (16.08%) and 4 were ambidextrous (2.01%; Table 2.1). Thirty nine patients with congenital anomalies involving unconventional aortic arch branching patterns were identified. These branching variants included the "bovine arch" (*n* = 30; 15.08%), an aberrant left vertebral artery (*n* = 5; 2.51%), and an aberrant right subclavian artery (*n* = 2; 1.01%). Two further rare branching variants were identified in two participants. In one participant the left subclavian artery branched off of the LCCA; and another had an aberrant right subclavian artery in combination with a "bovine arch" pattern (Figure 2.1).

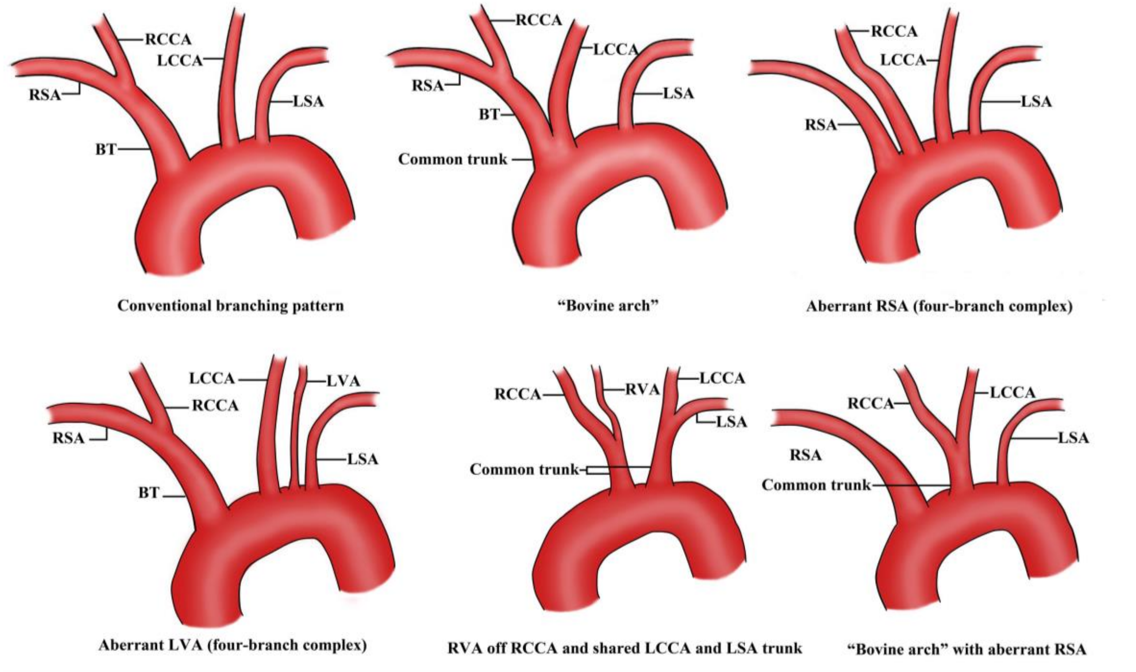

Figure 2.1. Schematic drawings of six aortic branching variations found in the sample population. RSA= right subclavian artery; LSA= left subclavian artery; RVA= right vertebral artery; LVA= left vertebral artery.

Conventional Branching Patterns

A total of 150 participants (136 right-handed, 20 left-handed, 4 ambidextrous) were identified with a conventional aortic arch branching pattern and were included in the analyses. Coronal, sagittal, and axial views of the CTAs of one right-handed and one left-handed participant with normal aortic branching patterns visually illustrate the geometric variability of the LCCA and the RCCA-BT complex (Figure 2.2).

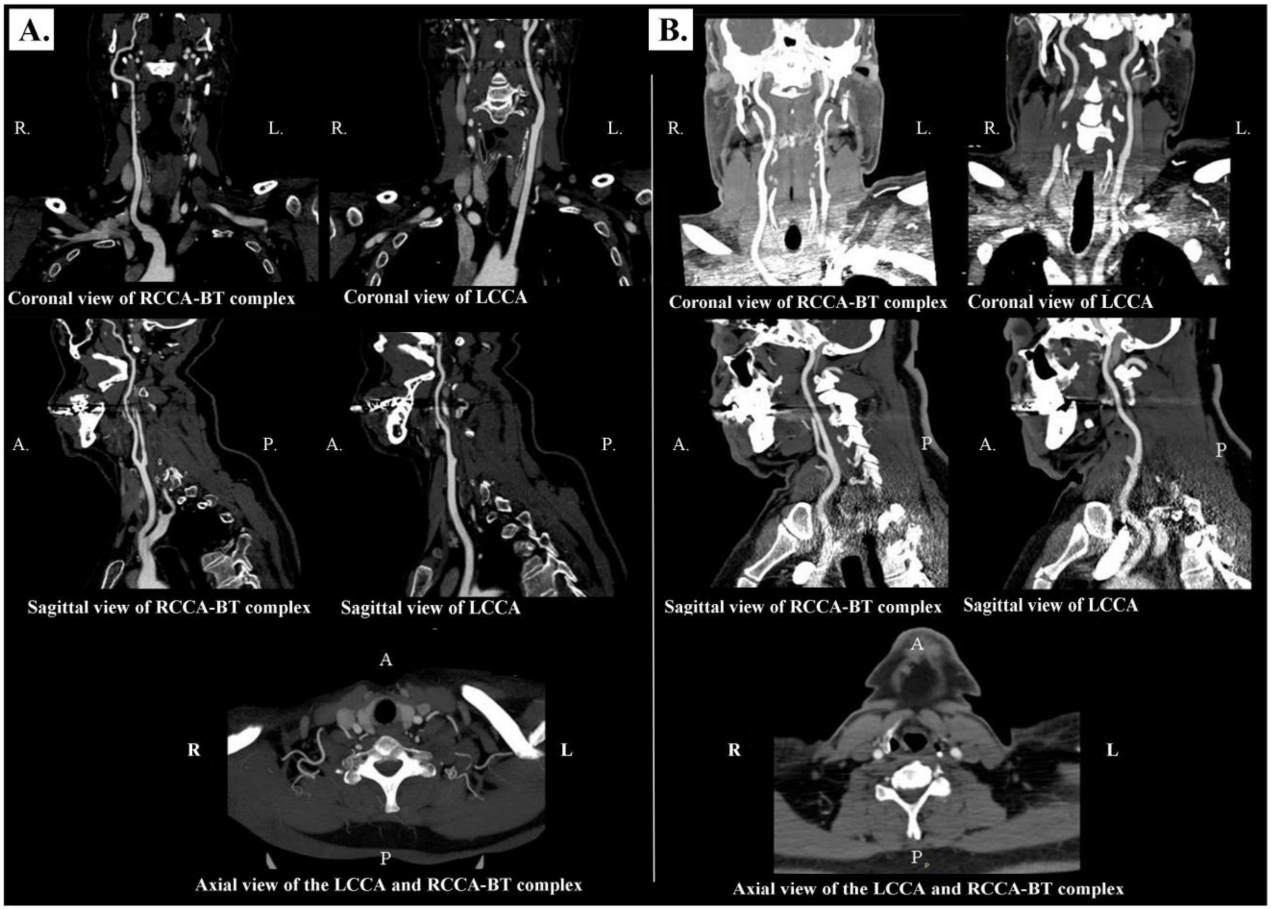

Figure 2.2. Coronal, sagittal, and axial projection from contrast-enhanced CTAs of LCCA and the RCCA-BT complex of one right-handed (A), and one left-handed (B) participant with conventional branching patterns.

Sex differences. Significant sex differences were found in two geometric parameters. Arterial lengths were significantly smaller in females than in males (Female *M* = 123.85mm; *SD* = 1.90; Male *M* = 134.61mm, *SD* = 1.33; $F(1, 158)= 21.62$, $p < .001$, $\eta p^2 = .120$). Similar results were found for D_{MAX} (Female *M* = 10.77mm, *SD* = 0.26; Male *M* = 11.64, *SD* = 0.18, $F(1, 158)= 7.50$, $p = .007$, $\eta p^2 = .045$). No significant differences were found for D_{MIN}, angle measures, or for arterial resistance.

Vessel length. In right-handers, vessel lengths were significantly larger on the right side (*M* = 136.44mm; *SD* = 15.71) than on the left (*M* = 125.92mm; *SD* = 14.20), $t(135) = -14.54$, $p < .001$, $d = .70$ (Table 2.2). However, side-to-side differences in left-handers and ambidextrous participants were negligible.

A significant main effect for CCA lengths was found — with a higher overall vessel length (averaged across all participants) on the right side, $F(1, 157) = 35.38$, $p < .001$, $\eta p^2 = .175$ (Table 2.3). There was no significant main effect for handedness, $F(2, 157) = 0.85$, $p = .432$. There was, however, a significant interaction effect between length and handedness, $F(2, 157) = 7.95$, $p = .001$, $\eta p^2 = .092$ (Table 2.3). Therefore, the differences in vessel length differed significantly between handedness groups. This disordinal interaction is illustrated in Figure 2.3. Pairwise Bonferroni post-hoc tests failed to detect significant differences in LCCA length in this handedness interaction, possibly due to the small sample size of the ambidextrous group.

The average length of the BT across all participants was 41.48mm (*SD* = 7.93) — accounting for 30.49% of the RCCA-BT complex length. There were no significant differences between handedness groups.

Table 2.2

Descriptive statistics and one-tailed paired t-tests comparisons of hemodynamic parameters between the LCCA and RCCA-BT complex across handedness groups

	Artery	Right-handed M (*SD*)	Left-handed M (*SD*)	Ambidextrous M (*SD*)	Total M (*SD*)
Length (mm)	LCCA	125.92 (14.20)	130.57 (14.07)	115 (21.63)	126.22 (14.47)
	RCCA-BT	136.44 (15.71)	133.33 (18.27)	128.55 (17.06)	135.85 (16.04)
	p	.000*	.051	.053	-
D_{MIN} (mm)	LCCA	6.20 (0.93)	5.84 (1.03)	5.88 (0.89)	6.15 (0.95)
	RCCA-BT	5.88 (0.95)	6.55 (1.31)	6.83 (0.88)	5.99 (1.03)
	p	.000*	.000*	.011*	-
D_{MAX} (mm)[a]	LCCA	9.85 (1.90)	9.92 (1.52)	9.83 (1.55)	9.86 (1.84)
	RCCA-BT	12.83 (2.29)	13.52 (2.29)	13.20 (1.17)	12.93 (2.27)
	p	.000*	.000*	.357	-
DEV_{MEAN} (°)	LCCA	20.15 (8.20)	21.35 (6.51)	18.12 (2.82)	20.25 (7.91)
	RCCA-BT	26.83 (10.08)	27.94 (8.25)	23.71 (3.96)	26.89 (9.75)
	p	.000*	.000*	.031*	-
DEV_{SUM} (°)	LCCA	123.77 (79.48)	141.48 (65.11)	136.68 (27.46)	126.31 (76.95)
	RCCA-BT	198.92 (106.52)	187.33 (96.23)	195.45 (38.71)	197.38 (103.84)
	p	.000*	.001*	.084	-
A_{MEAN} (°)	LCCA	156.51 (13.93)	152.28 (14.63)	151.05 (4.72)	155.80 (13.93)
	RCCA-BT	144.54 (18.78)	145.13 (13.31)	142.77 (15.04)	144.57 (18.04)
	p	.000*	.028*	.159	-
A_{SUM} (°)	LCCA	168.35 (124.60)	190.22 (118.62)	214.50 (42.92)	172.24 (122.46)
	RCCA-BT	279.50 (167.37)	262.78 (142.96)	261.08 (89.30)	274.39 (162.49)
	p	.000*	.003*	.246	-
Resistance ($dyn.s.cm^{-5}$)[a]	LCCA	15.41 (10.92)	20.67 (11.66)	16.79 (10.50)	16.10 (11.08)
	RCCA-BT	21.45 (16.18)	14.41 (9.52)	10.12 (6.82)	20.29 (15.56)
	p	.000*	.000*	.031*	-

Note. $p < .05$; LCCA = Left common carotid artery; RCCA-BT = Right common carotid artery with Brachiocephalic trunk

[a] Wilcoxon signed-rank test was run on right-handed participants for these variables

Table 2.3

Effects of handedness on geometric parameters of the CCAs

	Source	*df*	*F*	*p*	ηp^2
Length	Length	1	33.38	.000*	.175
	Handedness	2	0.85	.432	.011
	Length*Handedness	2	7.95	.001*	.092
D_{MIN}	D_{MIN}	1	17.36	.000*	.100
	Handedness	2	0.42	.658	.005
	D_{MIN}*Handedness	2	35.04	.000*	.309
D_{MAX}	D_{MAX}	1	101.38	.000*	.392
	Handedness	2	0.26	.775	.003
	D_{MAX} *Handedness	2	1.52	.222	.019
DEV_{MEAN}	DEV_{MEAN}	1	22.96	.000*	.128
	Handedness	2	0.39	.677	.005
	DEV_{MEAN} *Handedness	2	0.05	.955	.001
DEV_{SUM}	DEV_{SUM}	1	24.79	.000*	.136
	Handedness	2	0.02	.984	.000
	DEV_{SUM} *Handedness	2	1.84	.163	.023
A_{MEAN}	A_{MEAN}	1	19.19	.000*	.109
	Handedness	2	0.25	.780	.003
	A_{MEAN} *Handedness	2	2.07	.130	.026
A_{SUM}	A_{SUM}	1	17.72	.000*	.101
	Handedness	2	0.03	.969	.000
	A_{SUM} *Handedness	2	1.83	.163	.023
Resistance	Resistance	1	2.03	.157	.013
	Handedness	2	0.33	.719	.004
	Resistance*Handedness	2	20.49	.000*	.207

Note. $p < .05$

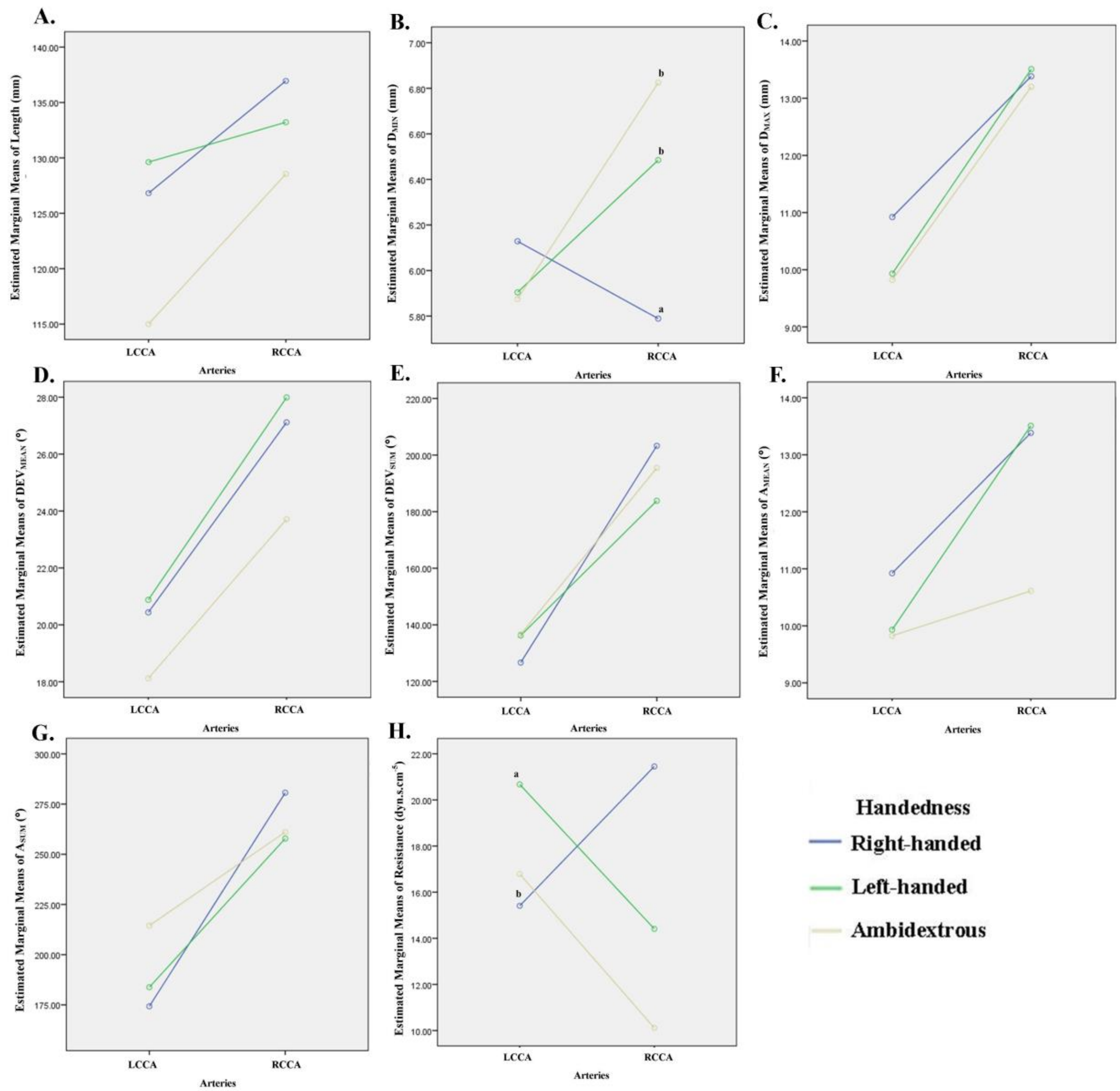

Figure 2.3. Interaction effects of CCA Length (A), D_{MIN} (B), D_{MAX} (C), DEV_{MEAN} (D), DEV_{SUM} (E), A_{MEAN} (F); A_{SUM} (G), Resistance (H), and handedness. Pairwise Bonferroni post-hoc test significance indicated by [ab].

Diameter measures. Diameter comparisons between the LCCA and the RCCA-BT complexes and between the handedness groups revealed significant asymmetries.

Minimum diameter. In right-handers, D_{MIN} was significantly greater on the left side (*M* = 6.20mm; *SD* = 0.93) than that on the right (*M* = 5.87mm; *SD* = 0.93), $t(135) = 6.49$, $p < .001$, $d = .34$, and the converse was seen in left-handers (LCCA *M* = 5.84; *SD* = 1.03; RCCA-BT *M* = 6.55mm; *SD* = 1.31), $t(19) = -5.02$, $p < .001$, $d = .61$ (Table 2.2). The same converse asymmetry was found in ambidextrous participants (LCCA *M* = 5.88mm; *SD* = 0.89; RCCA-BT *M* = 6.83mm; *SD* = 0.88), $t(3) = -4.34$, $p = .011$, $d = 1.07$.

A significant main effect for CCA D_{MIN} was found — with a larger overall vessel D_{MIN} (averaged across all participants) on the right side, $F(1, 157) = 17.36$, $p < .001$, $\eta p^2 = .100$ (Table 2.3). There was no significant main effect for handedness, $F(2, 157) = 0.42$, $p = .658$. There was, however, a significant interaction effect between D_{MIN} and handedness, $F(2, 157) = 35.04$, $p < .001$, $\eta p^2 = .309$ (Table 2.3). Therefore, the differences in vessel D_{MIN} differed significantly between handedness groups. This disordinal interaction is illustrated in Figure 2.3. Pairwise Bonferroni post-hoc test showed a significant difference in RCCA-BT complex D_{MIN} between left- and right-handers in this handedness interaction, $p = .006$ (Figure 2.3), with a significantly smaller D_{MIN} on the right side in right-handers.

Maximum diameter. In right-handers, D_{MAX} were significantly larger on the right side (*M* = 12.83mm; *SD* = 2.29) than on the left (*M* = 9.85mm; *SD* = 1.89), $T = 42.00$, $p < .001$, $r = 0.86$. The same was seen in left-handers (RCCA-BT *M* = 13.52mm; *SD* = 2.29; LCCA *M* = 9.92mm; *SD* = 1.52), $t(19) = -9.17$, $p < .001$, $d = 1.89$ (Table 2.2). Side-to-side differences in ambidextrous participants were negligible.

A significant main effect for CCA D_{MAX} was found — with a higher overall vessel D_{MAX} (averaged across all participants) on the right side, $F(1, 157) = 101.38$, $p < .001$, $\eta p^2 = .392$ (Table 2.3). There was no significant main effect for handedness or handedness interactions between the D_{MAX} of the CCA arteries of the different handedness groups (Figure 2.3).

Arterial angle measures. There were significant asymmetries of vessel angles between the LCCA and the RCCA-BT complex. These asymmetries were found in accumulative angle deviation, mean angle deviation, and mean artery angle, and total accumulative artery angle.

Artery angle deviation from vertical. In right-handers, DEV_{MEAN} was significantly larger on the right side (M = 26.83°; SD = 10.07) than on the left (M = 20.15°; SD = 8.20), $t(135)= -10.61$, $p < .001$, $d = 0.73$. The same was seen in left-handers (RCCA-BT M = 27.95°; SD = 8.24; LCCA M = 21.35°; SD = 6.51), $t(19)= -5.23$, $p < .001$, $d = 0.89$, and ambidextrous participants (RCCA-BT M = 23.71°; SD = 3.96; LCCA M = 18.12°; SD = 2.82), $t(3)= -2.94$, $p = .031$, $d = 3.39$ (Table 2.2).

A significant main effect for CCA DEV_{MEAN} was found — with a higher overall vessel DEV_{MEAN} (averaged across all participants) on the right side, $F(1, 157)= 22.96$, $p < .001$, $\eta p^2 = .128$ (Table 2.3). There was no significant main effect for handedness or handedness interactions between the DEV_{MEAN} of the CCA arteries of the different handedness groups. Similar findings were reflected in DEV_{SUM} measures, with the exception that side-to-side differences in ambidextrous participants were negligible (Table 2.2; 2.3).

Artery curvature. In right-handers, A_{MEAN} was significantly larger (indicative of straighter arteries) on the left side (M = 156.51°; SD = 13.93) than on the right (M = 144.53°; SD = 18.78), $t(135)= 13.41$, $p < .001$, $d = 0.73$. The same was seen in left-handers (RCCA-BT M = 152.28°; SD = 14.63; LCCA M = 145.13°; SD = 13.31), $t(19)= 2.03$, $p = .028$, $d = 0.93$ (Table 2.2). Side-to-side differences in ambidextrous participants were negligible.

A significant main effect for CCA A_{MEAN} was found — with a higher overall vessel A_{MEAN} (averaged across all participants) on the left side, $F(1, 157)= 19.19$, $p < .001$, $\eta p^2 = .109$ (Table 2.3). There were no significant main effects for handedness or handedness interactions between the A_{MEAN} of the CCA arteries of the different handedness groups (Table 2.3 and Figure 2.3).

Similar findings were reflected in A_{SUM} measures, indicating greater overall arterial curvature in the RCCA-BT complex across all handedness groups (Table 2.2; 2.3).

Resistance to blood flow. In right-handers, vessel resistance was significantly greater on the right side (M = 21.45dyn.s.cm^{-5}; SD = 16.18) than that on the left (M = 15.40dyn.s.cm^{-5}; SD = 10.92; T = 863.00, $p < .001$, r = 0.71), and the converse was seen in left-handers (RCCA-BT M = 14.41dyn.s.cm^{-5}; SD = 9.52; LCCA M = 20.67dyn.s.cm^{-5}; SD = 11.66), t(19)= 3.79, $p < .001$, d = 0.59. The same converse relationship was seen in ambidextrous participants (LCCA M = 16.79dyn.s.cm^{-5}; SD = 10.50; RCCA-BT M = 10.12dyn.s.cm^{-5}; SD = 6.82), t(3)= 2.91, p = .031, d = 3.36 (Table 2.2).

No significant main effects for CCA resistance, F(1, 157)= 2.03, p = .157, or for handedness was found, F(2, 157)= 0.33, p = .719 (Table 2.3). There was, however, a significant interaction effect between arterial resistance and handedness, F(2, 157)= 49.66, $p < .001$, ηp^2 = .240 (Table 2.3). Therefore, the differences in vessel resistance differed significantly between handedness groups. This disordinal interaction is illustrated in Figure 2.3. A Pairwise Bonferroni post-hoc test showed a significant difference in LCCA resistance between left- and right-handers in this handedness interaction, p = .048 (Figure 2.3), with a significantly higher resistance on the left side in left-handers.

Discriminant Function Analysis

A discriminant function analysis was conducted to assess whether arterial resistance could accurately classify an individual's handedness (i.e. right-handed or left-handed). The analysis only included participants with conventional branching patterns.

The resulting discriminant analysis significantly differentiated the handedness groups, Λ = .733, χ^2 (2)= 34.49, $p < .001$. Tests of equality of group means and an evaluation of the structure matrix revealed that the resistance in both arteries significantly contributed to the classification, RCCA-BT (-.281) and LCCA (.296) (Table 2.4). Therefore, the variability of the arteries feeding both hemispheres significantly differentiates the handedness groups. The cross-validated classification showed that overall 89.7% of cases were correctly classified — with accurate group membership predictions for 97.1% of right-handers and 40% of left-handers (Table 2.5).

The following discriminant equation results:

D = (6.416 × LCCA resistance) + (-4.534 × RCCA resistance) -.246

Table 2.4.

Tests of equality of group means and structure matrix of resistance's contribution to the model

	Artery	Function	Wilks' Lambda	*F*	*df1*	*df2*	*p*
Resistance	LCCA	.296	.977	3.98	1	154.000	.048*
	RCCA-BT	-.281	.975	22.53	2	153.000	.000*

Note. $p < .05$

Table 2.5.

Resistance to blood flow classification table

			Predicted group membership		
		Handedness	Right-handed	Left-handed	Total
Original[a]	Count	Right-handed	132	4	136
		Left-handed	12	8	20
	%	Right-handed	97.1	2.9	100
		Left-handed	60	40	100
Cross-validated[b,c]	Count	Right-handed	132	4	136
		Left-handed	12	8	20
	%	Right-handed	97.1	2.9	100
		Left-handed	60	40	100

[a] 89.7% of original grouped cases correctly classified.
[b] Cross validation is done only for those cases in the analysis. In cross validation, each case is classified by the functions derived from all cases other than that case.
[c] 89.7% of cross-validated grouped cases correctly classified.

Geometric Changes with Age

Interesting age-related trends for left- and right-handers were identified for arterial geometry (Table 2.6 and Figure 2.4). There were no significant relationships between arterial lengths and age for either handedness group (Table 2.6). In right-handers, however, diameter measures in both arteries demonstrated statistically significant arterial dilation with increasing age. More specifically these age-related relationships were identified in D_{MIN} (LCCA R^2 = .078, p = .001; RCCA-BT R^2 = .041, p = .017) and D_{MAX} (LCCA R^2 = .034, p = .033; RCCA-BT R^2 = .087, p < .001). As a consequence to bilateral arterial dilation, right-handers also demonstrated a significant decrease in resistance to blood flow with increasing age (LCCA R^2 = .103, p < .001; RCCA-BT R^2 = .056, p = .006). Left-handers, on the other hand, showed no significant age-related relationships for these variables (Table 2.6). These trends are visually illustrated in Figure 2.4.

In both handedness groups arterial curvature increased significantly with increasing age (Figure 2.4). More specifically, right-handers demonstrated significant positive age-related relationships for DEV_{SUM} (LCCA R^2 = .285, p < .001; RCCA-BT R^2 = .278, p < .001) and A_{SUM} (LCCA R^2 = .267, p < .001; RCCA-BT R^2 = .324, p < .001); and left-handers showed significant positive significant age-related relationships for DEV_{SUM} (LCCA R^2 = .388, p = .020; RCCA-BT R^2 = .269, p = .001) and A_{SUM} (LCCA R^2 = .265, p = .003; RCCA-BT R^2 = .439, p = .019). These trends are visually illustrated in Figure 2.4.

Importantly, no side-to-side differences and age-related relationships were found for any of the handedness groups, as determined by the overlapping confidence intervals between the arteries of each handedness group for each geometric measure (Table 2.6).

Table 2.6.

Regression analyses of geometric variables and age for left- and right-handers with a conventional aortic arch branching pattern

			Unstandardized coefficients		Standardized coefficients			95% confidence interval for *B*	
Geometric parameter	Handedness	Artery	*B*	*SE B*	β	*t*	*p.*	*Lower Bound*	*Upper Bound*
Length	Right-handed	LCCA	0.04	0.11	0.03	0.35	.724	-0.19	0.27
		RCCA-BT	0.12	0.10	0.10	1.18	.240	-0.08	0.33
	Left-handed	LCCA	0.38	0.29	0.29	1.28	.215	-0.24	0.99
		RCCA-BT	0.20	0.23	0.20	0.87	.395	-0.28	0.69
D_{MIN}	Right-handed	LCCA	5.64	1.67	0.28	3.38	.001*	2.34	8.94
		RCCA-BT	4.01	1.67	0.20	2.41	.017*	0.72	7.31
	Left-handed	LCCA	0.66	4.19	0.04	0.16	.877	-8.15	9.46
		RCCA-BT	3.60	3.18	0.26	1.13	.272	-3.08	10.28
D_{MAX}	Right-handed	LCCA	1.82	0.84	0.18	2.16	.033*	0.15	3.48
		RCCA-BT	2.43	0.68	0.30	3.57	.000*	1.08	3.77
	Left-handed	LCCA	-1.95	2.78	-0.16	-0.70	.491	-7.78	3.88
		RCCA-BT	-0.98	1.83	-0.13	-0.54	.599	-4.83	2.87
DEV_{SUM}	Right-handed	LCCA	0.13	0.02	0.53	7.31	.000*	0.09	0.16
		RCCA-BT	0.09	0.01	0.53	7.19	.000*	0.07	0.12
	Left-handed	LCCA	0.18	0.05	0.62	3.38	.003*	0.07	0.28
		RCCA-BT	0.10	0.04	0.52	2.57	.019*	0.02	0.18
A_{SUM}	Right-handed	LCCA	.076	.011	.505	6.780	.000*	.054	.099
		RCCA-BT	.064	.008	.569	8.007	.000*	.048	.080
	Left-handed	LCCA	.079	.031	.515	2.547	.020*	.014	.145
		RCCA-BT	.085	.023	.662	3.751	.001*	.037	.132
Resistance	Right-handed	LCCA	-0.55	0.14	-0.32	-3.93	.000*	-0.83	-0.28
		RCCA-BT	-0.28	0.10	-0.24	-2.82	.006*	-0.47	-0.08
	Left-handed	LCCA	0.20	0.37	0.13	.53	.591	-0.57	0.97
		RCCA-BT	-0.49	0.44	-0.25	-1.11	.283	-1.40	0.44

Note. $p < .05$

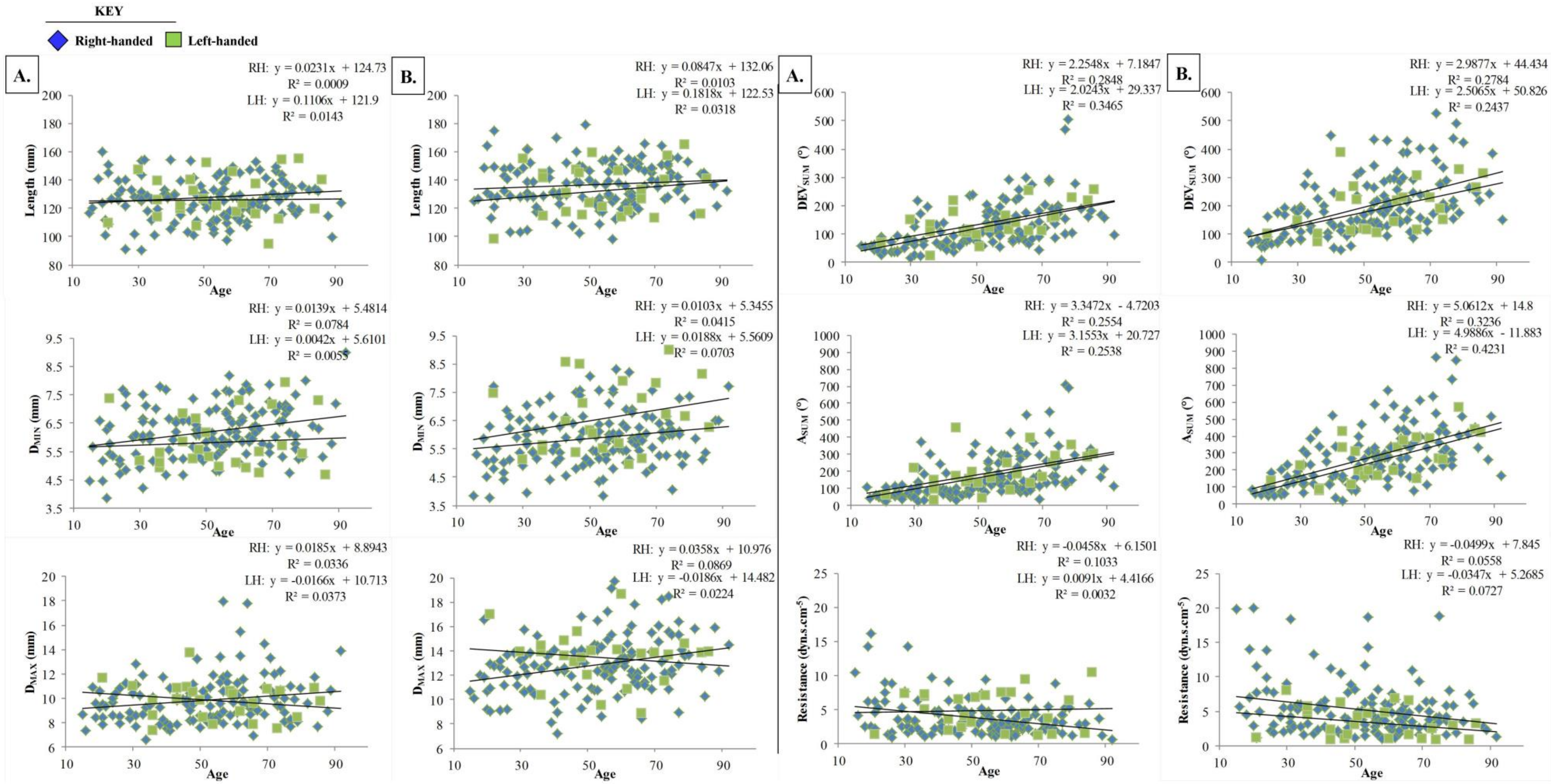

Figure 2.4. Scatterplots of the relationship between LCCA (A), and RCCA-BT complex (B) geometric measures and age in left-and right-handers with a conventional aortic branching pattern

Unconventional Branching Patterns

Bovine arch. Twenty eight right-handed participants were identified with a "bovine arch" branching pattern (Figure 2.5). No significant differences in total arterial lengths, BT lengths, arterial curvatures, or resistances were found between these participants and those with a conventional branching pattern (Table 2.7). Due to the nature of branching of the "bovine arch", where the LCCA and the RCCA share a common origin, the D_{MAX} measures of both vessels were the same (M = 16.76, SD = 2.81). These were significantly larger than the D_{MAX} of the RCCA-BT complex of participants with a conventional branching pattern, $U = 517$, $z = -6.06$, $p < .001$, $r = -0.48$.

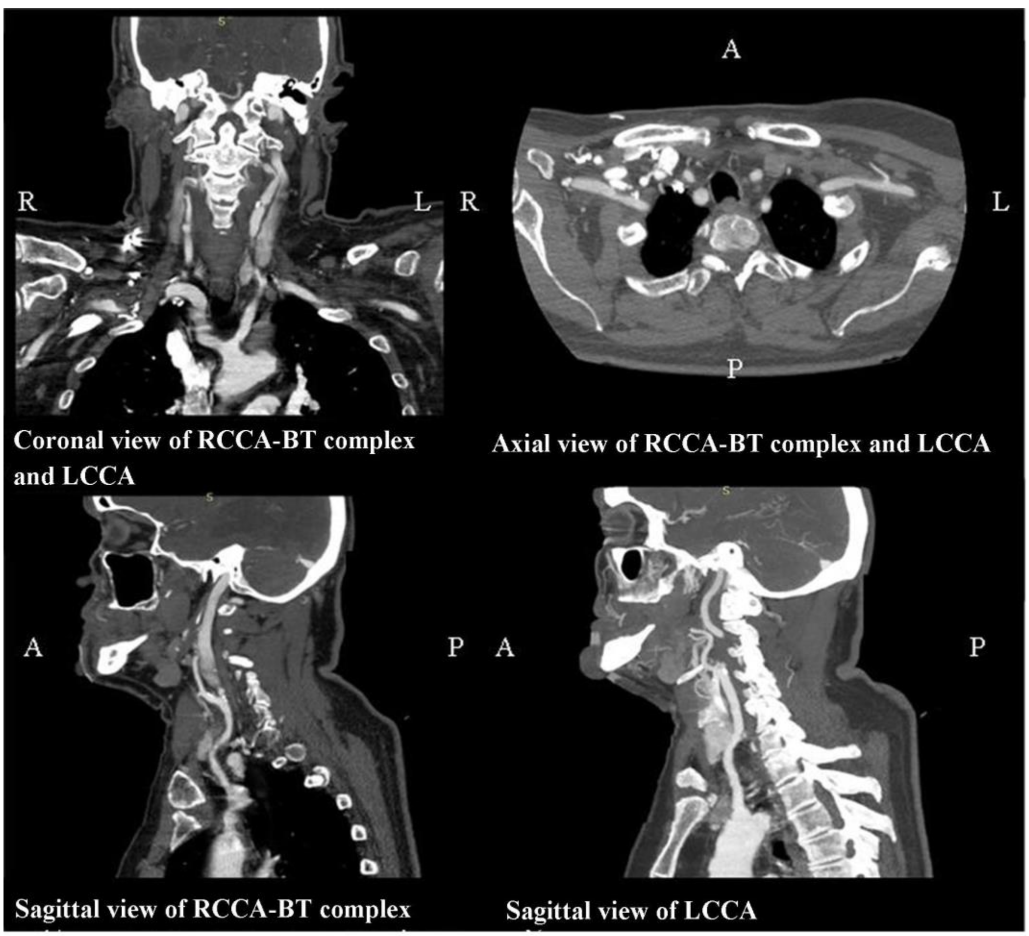

Figure 2.5. Coronal, sagittal, and axial projection from contrast-enhanced CTAs of the RCCA-BT complex in a right-handed participant with a "bovine arch" branching pattern.

Further differences were found in D_{MIN} — where the RCCA-BT complex (*M* = 5.45mm, *SD* = 1.07) was significantly smaller in the "bovine arch" branching group than those in the conventional branching group, $t(162) = 2.13$, $p = .035$, $d = 1.27$ (Table 2.7). Consequently, participants still demonstrated a significant handedness asymmetry in D_{MIN}, $t(27) = 5.68$, $p < .001$, $d = 0.44$, that contributed to greater arterial resistance in the RCCA-BT complex, $t(27) = -2.94$, $p = .007$, $d = 1.13$.

Table 2.7

Geometric comparisons between conventional and "Bovine arch" branching variants in right-handed participants.

Geometry	Arteries	Conventional M (*SD*)	Bovine arch M (*SD*)	*t/U*	*Df*	*p*
Length (mm)	LCCA	125.92 (14.20)	130.38 (17.53)	-1.45	162	.148
	RCCA-BT	136.44 (15.71)	138.66 (17.43)	-0.67	162	.504
	BT	40.95 (7.89)	43.82 (7.07)	-1.78	162	.076
D_{MIN} (mm)	LCCA	6.20 (0.93)	5.93 (1.13)	1.34	162	.181
	RCCA-BT	5.88 (0.95)	5.45 (1.07)	2.13	162	.035*
D_{MAX} (mm)[a]	LCCA	9.85 (1.90)	16.76 (2.81)	197.50	162	.000*
	RCCA-BT	12.82 (2.29)	16.76 (2.81)	517	162	.000*
DEV_{MEAN} (°)	LCCA	20.15 (8.20)	21.98 (7.65)	-1.08	162	.281
	RCCA-BT	26.83 (10.08)	27.52 (9.82)	-0.33	162	.740
DEV_{SUM} (°)	LCCA	123.77 (79.48)	136.96 (86.01)	-0.79	162	.432
	RCCA-BT	198.92 (106.52)	217.64 (123.30)	-0.82	162	.411
A_{MEAN} (°)	LCCA	156.51 (13.93)	154.25 (13.17)	0.79	162	.433
	RCCA-BT	144.54 (18.79)	144.85 (13.49)	-0.08	162	.933
A_{SUM} (°)	LCCA	168.35 (124.60)	189.03 (125.05)	-0.80	162	.425
	RCCA-BT	276.50 (167.37)	293.53 (149.31)	-0.05	162	.618
Resistance (dyn.s.cm^{-5})[a]	LCCA	15.41 (10.92)	21.91 (19.94)	1591	162	.172
	RCCA-BT	21.45 (16.18)	35.08 (37.05)	1507	162	.142

Note. $p < .05$; [a] Non-parametric Mann-Whitney U test was run for these variables.

Only two left-handed participants were identified with a “bovine arch” branching variant. Due to the small number in this group, no statistical analyses could be run. Despite this, some interesting results were observed (Figure 2.6). Although length measures were similar between the two groups, the BT was longer in participants with a “bovine arch” (*M* = 50.4mm, *SD* = 11.88) as opposed to those with a conventional branching pattern (*M* = 42.48mm, *SD* = 9.45). As expected, the D_{MAX} measures of both vessels were the same (*M* = 13.55mm, *SD* = 2.62) and were larger than the D_{MAX} of the RCCA-BT complex in the conventional branching group. D_{MIN} showed an inverse relationship to left-handers with conventional branching patterns — with a larger D_{MIN} on the right (*M* = 6.15mm, *SD* = 1.62) than on the left (*M* = 6.68mm, *SD* = 1.24). Resistance values were smaller than the conventional branching group and mirrored the inverse relationship found in diameter measures — with a higher resistance on the right (*M* = 18.32dyn.s.cm^{-5}, *SD* = 15.56); than on the left (LCCA *M* = 10.38dyn.s.cm^{-5}, *SD* = 6.32) $T = 5$, $p < .001$, $r = 0.85$. Variability in angle measures was large. Consequently, no conclusions could be drawn regarding branching differences. It is important, however to interpret these asymmetries with caution as they only reflect qualitative differences in two participants.

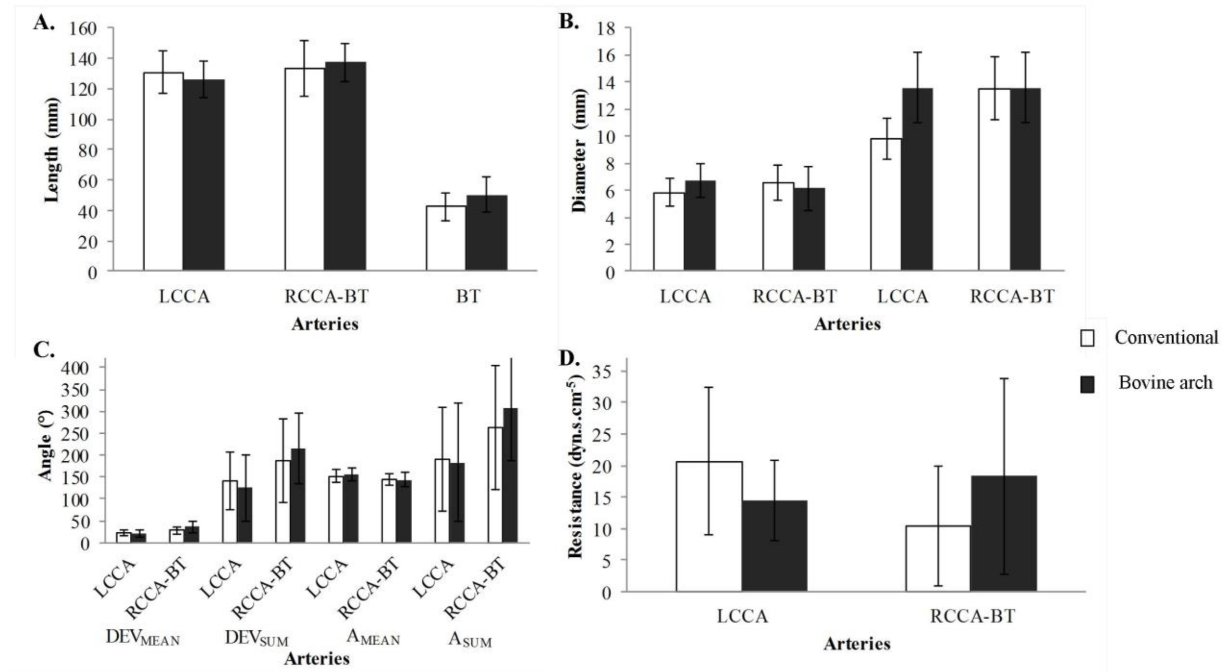

Figure 2.6. Differences between arterial length (A), diameter (B), angle (C), and resistance measures between left-handed participants with a conventional aortic arch branching pattern and those with a "bovine arch"

Aberrant left vertebral artery. Only 4 right-handed participants showed an unconventional aortic arch branching pattern characterised by an aberrant left vertebral artery. Due to the small number in this group, no statistical analyses could be run and only qualitative differences were noted between the groups (Figure 2.7). D_{MIN} of the LCCA (M = 5.49mm, SD = .68) and the RCCA-BT complex (M = 5.28mm, SD = 0.52), and D_{MAX} of the LCCA (M = 8.63mm, SD = 2.40) and the RCCA-BT complex (M = 11.79mm, SD = 1.93), were smaller than those with conventional branching patterns (Figure 2.7). This predicts a higher resistance to blood flow within the two vessels which still maintains the handedness asymmetry of the conventional branching group. This is supported by resistance calculations (LCCA M =

21.77dyn.s.cm^{-5}, *SD* = 8.58; RCCA-BT complex *M* = 27.13dyn.s.cm^{-5}, *SD* = 7.11). Variability in angle measures was large. Consequently, no conclusions could be drawn regarding branching differences (Figure 2.7).

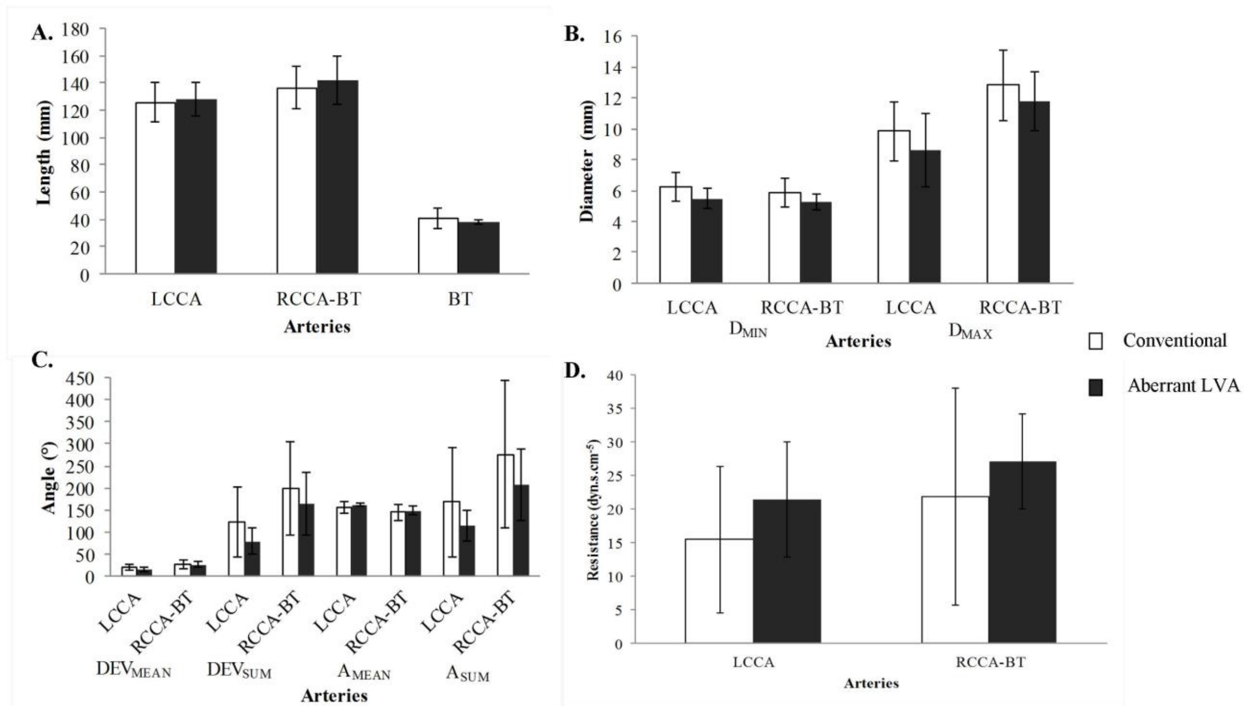

Figure 2.7. Differences between arterial length (A), diameter (B), angle (C), and resistance measures between right-handed participants with a conventional aortic arch branching pattern and those with an aberrant left vertebral artery

Aberrant right subclavian artery. Only 2 participants showed an unconventional branching variant where no BT was present, causing the RCCA to originate directly off the aortic arch. Despite the absence of statistical analyses, some interesting differences were observed (Figure 2.8). The lengths of the LCCA (*M* = 133.35mm, *SD* = 8.70) and the RCCA (*M* = 129.85mm, *SD* = 11.24) become almost indistinguishable in individuals with no BT due to an increased LCCA length. Similarly, the D_{MIN} (LCCA *M* = 6.05mm, *SD* = 1.20; RCCA *M* =

6.08mm, *SD* = 0.74), and the D_{MAX} (LCCA *M* = 8.05mm, *SD* = 1.34; RCCA *M* = 7.63mm, *SD* = 0.04), of the two arteries were alike, and were smaller than those with normal branching patterns. This predicts a more even resistance to blood flow between the two vessels. Variability in angle measures was large. Consequently, no conclusions could be drawn regarding branching differences. Importantly, these observations must be interpreted with caution.

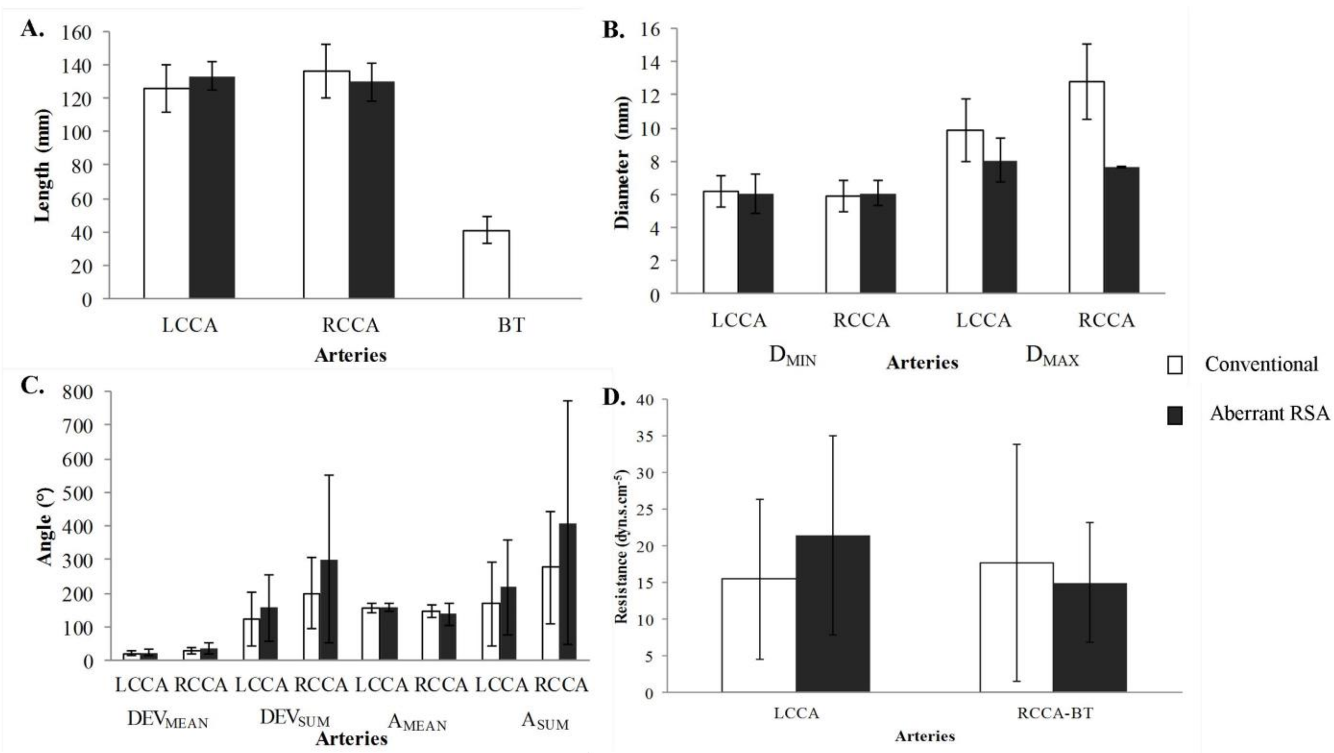

Figure 2.8. Differences between arterial length (A), diameter (B), angle (C), and resistance measures between right-handed participants with a conventional aortic arch branching pattern and those with an aberrant right subclavian artery

Inclusion of all branching patterns. The inclusion of all participants with unconventional branching patterns into the main analysis (involving paired t-tests and mixed-design ANOVAs of conventional branching patterns) resulted in only two notable changes to the findings. First, the difference in vessel lengths of left-handed participants became statistically significant. This occurred in the same direction as the asymmetry previously established in right-handers (RCCA-BT *M* = 133.22mm; *SD* = 17.35; LCCA *M* = 129.62mm; *SD* = 13.65), $t(22) = -2.44$, $p = .012$, $d = 0.23$. Second, a significant interaction between D_{MAX} and handedness was revealed, $F(2, 196) = 3.60$, $p = .029$, $\eta p^2 = .035$. Therefore, the differences in vessel D_{MAX} differed significantly between handedness groups. However, Pairwise Bonferroni post-hoc tests failed to identify significant differences within this significant interaction effect.

It is important to note, however, that the handedness interactions found in D_{MIN}, length and arterial resistance in the main analysis was maintained in this secondary analysis — further validating the presence of the geometric handedness asymmetries established in this chapter.

Discussion

Functional and morphological asymmetries of the brain are well established in the literature (Witelson, 2012). Akin to these asymmetries, differences in cerebral perfusion have been noted. While right-handers have increased blood flow in the left hemisphere in order to satisfy the increased metabolic demand, left-handers are more active in the right hemisphere (Vivani et al., 1998). Given that large arteries regulate cerebral blood flow, an investigation of the geometry of these arteries and of blood flow asymmetries is essential (Magun, 1973).

This chapter provided a systematic quantification of the geometric properties of the CCAs between handedness groups. This sample accords with normative data regarding handedness distribution (Rife, 1940; Oldfield, 1971, Thilers et al., 2007), CCA structure (Avolio, 1980), the incidence of aortic arch branching variants (Alsaif & Ramadan, 2010; Gupta & Sodhi, 2005; Jakanani & Adair, 2010), and sex-related data (Vuoksimaa et al., 2009).

Results confirm considerable asymmetries between the geometric properties of the LCCA and RCCA-BT complex in different handedness groups. These handedness asymmetries were evident in arterial minimum diameter and length, and are validated by high effect sizes in the data. Consequently, these findings are indicative of significantly higher arterial resistance on the side contralateral to the dominant hemisphere. Right-handed subjects demonstrated increased blood flow resistance in the RCCA-BT complex, while left-handed participants showed higher blood flow resistance in the LCCA. Since flow and resistance are reciprocally related, an increase in resistance decreases flow at any given change in arterial pressure, these asymmetries therefore reflect a disparity in blood flow (Nichols, & O'Rourke, 1998). Ambidextrous participants mirrored the geometry of left-handers for minimum diameter, length and resistance measures.

While 85.29% of right-handers showed lower resistances in the arterial structures feeding the left hemisphere, 90% of left-handers and 100% of ambidextrous individuals showed lower resistances on the right. Nevertheless, the present study shows that arterial resistance is on average 43.98% lower on the left in right-handers. Conversely, arterial resistance on the right is on average 30.66% lower in left-handers and 36.55% lower in ambidextrous participants. These findings are in keeping with asymmetries found in the literature (Lehman, & Benjain, 1995-1998; Müller et al., 1991; Ogle, 1871).

Shin et al. (2008) conclude that the average angles at which the major branches arise from the aortic arch are much larger in the BT than in the LCCA. Although angle deviations at the origin of the aortic arch were not investigated in isolation here, significantly higher vessel curvatures were found in the RCCA-BT complex versus the LCCA in both right-handed and left-handed individuals.

The influence of arterial curvature on blood flow is not completely understood (Manbachi et al., 2011). It seems, however, that secondary flows are caused by bifurcations or high curvatures in large calibre vessels. This contributes to the formation of localised low or oscillating wall shear stress, rather than effecting blood flow volume directly (Johnston & Johnston, 2007; Malek et al., 1999). At mild to high velocities, the combination of high curvature and a small vessel radius, produce a higher degree of velocity profile skewing and sheer stress than from the effects of radius and curvature alone (Johnston & Johnston, 2007; Myers, Moore, Ojha, Johnston, & Ethier, 2001). It seems therefore that the geometric environment of the RCCA in right-handers could play a pivotal role in the asymmetrical presence of skewed velocity profiles and secondary flows in the vessel. This would, however need to be directly investigated.

The results of this chapter contradict those authors who describe larger diameters in the RCCA (Manbachi et al., 2011), and lower vessel curvatures (Manbachi et al., 2011) and longer lengths (Ribeiro, Ribeiro, Rodrigues Filho, Caetano & Fazan, 2006) in the LCCA. However, these earlier studies used small sample sizes, failed to investigate minimum diameters, neglected to incorporate the BT, and made no comparisons between handedness groups. Therefore, an accurate comparison cannot be made between these findings and those of the present study.

Resistance in both the CCAs significantly differentiated between left- and right-handers. Ninety seven percent of right-handers and 40% of left-handers were correctly classified by the discriminant function analysis model. The low classification rate of left-handers is not surprising since the left-handed population is heterogeneous with respect to the direction of lateralisation, with approximately 60% being dominant in the left hemisphere (Roberts, 1969).

The study demonstrated significant age-related changes in arterial geometry. These included dilation of the arteries, decreased arterial resistance and increased vessel curvature. These age-related changes are in accordance with a large body of literature (Manbachi et al., 2011; McVeigh et al., 1999; Oxenham & Sharpe, 2003; Paulsen, Tillmann, Christofides, Richter, & Koebke, 2000, Scheel et al., 2000; Toda, Tsuda, Nishimori, Leszczynski, & Kummerow, 1980; Wensing et al. 1995).

Thirty nine patients with congenital anomalies involving unconventional aortic arch branching patterns were identified. Few geometric differences existed between right-handers with conventional branching patterns and those with a “bovine arch” variant. Despite the expected larger D_{MAX} — due to the common origin of the LCCA and BT in the “bovine arch” group, participants still demonstrated a significant handedness asymmetry with a higher resistance, longer length, and smaller diameter in the artery contralateral to hand dominance. Therefore, a handedness-related bias was still evident. It is noteworthy, however, that the increased calibre of the common origin of the “bovine arch” branching variant is not necessarily equivalent to the added cross-sectional area of the LCCA and BT of participants with a conventional branching pattern. It seems therefore that initial blood volumes entering into these vessels could be lower in participants with a “bovine arch” branching variant. Few participants showed further unconventional branching patterns and could therefore not be empirically assessed.

Implications

The left hemisphere dominance for manual dexterity and the localization of language-related functions in Broca’s and Wernicke’s areas, and the heteromodal association regions — which serve the most lateralized of functions — in combination with structural asymmetries, may all be effects of cerebral blood flow superiority in the left hemisphere (Chiron et al., 1997; Gur et al., 1982; Thatcher et al., 1987). However, this asymmetry only emerges after the first few years of life. Dominant cerebral perfusion switches from the right to the left in the sensorimotor region at approximately two and a half years of age (Chiron et al., 1997). This development is in concordance with the typical development of right-handedness and fine motor skills. A further perfusion shift in the multimodal parietotemporal region, from right to left, occurs at approximately three years of age (Chiron et al., 1997). This right-to-left sequential asymmetry seems to be related to the consecutive emergence of functions dedicated to the right (visuospatial abilities), and then to the posterior association cortex of the left (language abilities) hemispheres (Chiron et al., 1997).

Arterial geometry plays a key role in determining the nature of the haemodynamic properties of blood flow (Zhao et al., 2000). Although developmental asymmetries in carotid maturation have not been studied in relation to handedness, it is noteworthy that maximum, minimum and mean carotid flow rates increase steadily in infancy until ages two to four years, and the anatomical diameters increase accordingly (Kojo et al., 1996, Kojo et al., 1998).

It is possible that the handedness-related geometric asymmetry of the CCAs observed in this study is an effect rather than a cause of handedness, since increased flow is associated with thickening of vessel walls with age (Shaaban & Duerinckx, 2000), although lumen diameters adjust commensurately (Hansen et al., 1995). Many geometric variables demonstrated significant age-related changes in the study, and these differed between left- and right-handedness groups. More specifically, right-handers showed significant arterial dilation, increased vessel curvature and decreased resistance with increasing age, while left-handers only showed significant age-related trends for arterial curvatures. However, the lack of significance in the left-handed group could be attributed to the small size of the sample (n = 20). No side-to-side differences within each handedness group existed. In other words, the age-related changes identified by the regression analysis did not differ between the left and right CCAs. This indirectly suggests that the anatomical asymmetries reported here are not mediated by accumulating effects of asymmetrical top-down metabolic demands.

The consistent perfusion dominance of the left vertebral artery documented in the literature (Abd-el Bary et al., 1995; Mitchell, 2004; Seidel et al., 1999; Yuan et al., 1994) further suggests that the vascular asymmetry in bottom-up blood supply to the brain is independent of the top-down metabolic demand of the cerebral hemispheres. The vertebral arteries merge in the basilar artery before they supply the posterior cerebral arteries. It is therefore impossible that the leftward supply asymmetry observed at the level of the vertebral arteries is a response to top-down demand. This being the case (if the vertebral asymmetry is a matter of bottom-up supply) and given that the right vertebral and common carotid arteries arise from the same supply source, there is further indirect reason to infer that the observed CCA asymmetry is likewise a matter of bottom-up supply. However, developmental studies should be conducted to directly address this issue.

Chapter 3: Hemodynamic Characterisation

In order to holistic investigate arterial properties, knowledge of the arterial geometry, as well as a detailed characterisation of the physical factors that govern blood flow is essential — which typically quantifies time-averaged flow, waveform shape, arterial pressure, peak flow velocities, and flow volume rates (Badeer, 2001; Holdworth et al., 1999). The carotid artery is of special interest to many researchers because of the clinical importance of its complex flow properties. These studies pay particular attention to the site of the carotid bifurcation — which is characterised by turbulent flow and increased wall shear stress (Malek, Alper, & Izumo, 1999). Research indicates that as many as 30% of all major hemispheric events, which show a predilection for the left hemisphere, originate from disease at the carotid bifurcation (Rodriguez-Hernandez et al., 2003; Timsit et al., 1992). Due to the significant influence this bifurcation has on blood flow in the ICAs, it is essential to investigate the potential hemodynamic asymmetries both prior to and post the bifurcation.

Doppler ultrasound of the carotid arteries is the most common imaging examination performed for diagnosis of carotid artery disease world-wide — as the superficial location of the arteries allows for easy access by ultrasound to obtain geometric and flow data (Grant et al., 2003; Starmans-Kool et al., 2002). Among other hemodynamic measures, Doppler ultrasound has the ability to detect disturbed patterns of flow, mean blood flow rates, systolic peak velocities, and end-diastolic velocities within the centreline of the vessel in one complete cardiac cycle. It can further produce a quantitative graphic display of these measures (Bluth, Arger, Ralls, & Siegel, 2000).

Since cerebral blood flow is not only determined by the diameter of the vessel (Heron, 2012), but also by the velocity of the blood flow, a true understanding of extracranial carotid artery dominance can only be achieved by measuring blood flow volume (Cagnie et al., 2006). To further investigate the role of hemodynamics in handedness, it is therefore highly desirable to characterise the local hemodynamics of the left and right CCAs, as well as in the ICAs and ECAs at the bifurcation site relative to the tissue geometry. This allows for the quantification of the potential inherent asymmetries of this blood flow and its functional cerebral implications.

Specific Aims and Hypotheses

The following sub-hypothesis was examined:

H_1: The hemodynamic characteristics of the ICAs and CCAs facilitate increased blood flow in the artery contralateral to the dominant hand.

The following questions were addressed:

1. Are there significant hemodynamic differences between the left and right carotid arteries in left-handed versus right-handed individuals?
2. Can these variables predict handedness?
3. Is there a relationship between the hemodynamic characteristics of these arteries and the degree of hand-proficiency?

Design and Methods

Design and Setting

This study aimed to investigate cerebral asymmetrical blood flow and its relation to handedness. A non-experimental quantitative design was utilised, allowing for analysis of numerical data. This study was relational as it measured the potential relationships between handedness and multiple hemodynamic asymmetries of the left and right CCAs, ICAs, and ECAs. The variables were selected because of their strong characterisation of the hemodynamic properties of arterial blood flow. Analysis of the appropriate arteries took place at the Groote Schuur Hospital, where the potable Philips CX50 Ultrasound unit was stored.

Participants

Two hundred and thirty four healthy, normotensive volunteer subjects (174 right-handed; 54 left-handed; 6 ambidextrous), between the ages of 18 and 57 years (M = 24 years; SD = 7.08; 81 male and 153 female), were enrolled in the study (Table 3.1). The participants were recruited from Cape Town with the use of posters (Appendix C). A non-randomised participant sampling approach was used. Extensive exclusion criteria were adopted to ensure that the results were not confounded by extraneous variables (see below).

Participants were divided into the handedness categories based on a LQ generated by a revised version of the Edinburgh Handedness Inventory. The same classification parameters were used as for the geometric analysis in Chapter 2. The sample was representative of a young and healthy population which minimised the risk of including participants with age related cardiovascular disorders (Mitchell, 2002; Oxenham & Sharpe, 2003).

Hand-proficiency was measured through the administration of Speed and Accuracy Target Tests. Variability in hand-proficiency of participants through measures of Target scores is visually illustrated in Figure 3.1.

Table 3.1

Descriptive statistics for participants as a function of handedness

		Right-handed	Left-handed	Ambidextrous	Total
N		174	54	6	**234**
Sex (%)	Male	31.6	38.9	50	**34.6**
	Female	68.4	57.4	50	**65.4**
Age (SD)		23.61 (6.92)	24.44 (6.67)	30.83 (12.073)	**23.99 (7.08)**
TI (SD)	Speed	-0.23 (0.09)	0.21 (0.08)	0.07 (0.15)	**-1.22 (0.21)**
	Accuracy	0.11 (0.07)	-0.07 (0.06)	-.00 (0.06)	**.062 (0.10)**

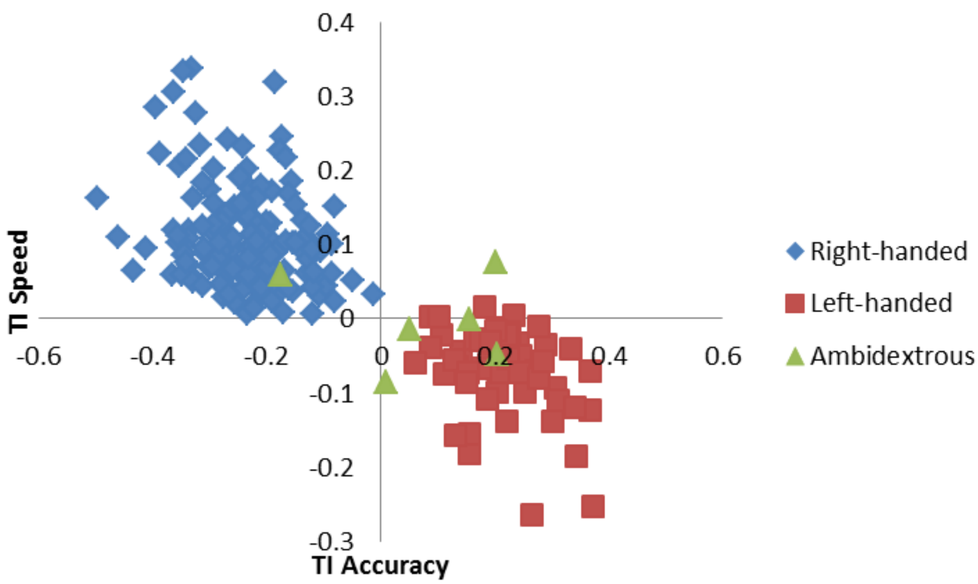

Figure 3.1. Distribution of Speed and Accuracy TI scores of handedness groups

Exclusion criteria. All subjects with pre-existing neurological and psychiatric disorders were removed from the study. Participants with a history of smoking, cardiovascular disease, pathological vascular abnormalities of the carotid arteries (including atherosclerotic disease, arterial stenosis, aneurysm, arterial dissections and other traumatic vascular injuries), hypertension (>140/90mmHg), hypercholesterolemia, diabetes mellitus, or who are on anti-inflammatory or other relevant drugs were also removed.

Materials

Ultrasound measurements. Cardiovascular imaging was performed using the portable Phillips CX50 unit stored at the vascular laboratory at Groote Schuur Hospital, Cape Town.

Imaging software. Philips CX50 Ultrasound system software: 453561459621 was used for the analysis of the ultrasound data.

Blood pressure. Blood pressure (BP) was taken using the Kingyield BP101H Digital Blood Pressure Monitor.

Revised Edinburgh Handedness Inventory. Hand-preference was assessed using a verbal administration of the same revised version of the Edinburgh Handedness Inventory seen in the geometric analysis (Appendix A and B). Scores obtained from this inventory formed a participant specific LQ, which ranged from 0 (all left) to 50 (all right) (Oldfield, 1975).

Target Tests. Hand-proficiency was assessed through the administration of a simple paper-and-pencil formatted test of manual speed and accuracy (Apendix E; Borod, Koff, & Caron, 1984). This provides direct behavioural assessment of unpractised motor acts. Target scores are substantially correlated with the Harris Tests of Lateral Dominance (1958) and other indices of laterality, and is therefore a reliable and valid measure of motoric lateral dominance, especially in research (Borod, Koff, & Caron, 1984).

Procedure

All measurements were performed after subjects underwent 10 min of supine rest in a quiet room without auditory or visual distractions, with constant illumination and comfortable room temperature (20-24°C). The subjects were required to abstain from caffeine, alcohol, and vigorous exercise for 24h prior to the assessment.

Doppler Ultrasound. Standard medical procedure was followed during the ultrasound analysis — taking approximately 15 minutes each. Doppler ultrasound was performed by a vascular technician, ensuring accurate and reliable data acquisition. This also guaranteed that the author remained blind to the hemodynamic readings during the hand-preference and proficiency tests.

After the participant had remained in supine position for the stipulated time frame, they were instructed to slightly hyperextend their head and rotate it 45° contralateral to the side being examined. A clear water based gel was applied to the neck (the area directly overlying the carotid arteries). This ensured secure contact between the body and the low frequency transducer (< 7 Hz). The transducer was then firmly pressed against the skin of the neck of the participant, without compression, to prevent the introduction of artificial errors in vascular resistance — starting from the proximal aspect of the CCA moving distally.

An initial two-dimensional B mode Grey-Scale Imaging screening was performed in the sagittal plane, for artery identification and screening for the presence of any arterial pathology. If no pathology was present, Pulsed-wave Doppler examinations were performed on the longitudinal sections of the imaged artery. The size of the sample volume was set to 2mm and was positioned at the centre of the vessel approximately 2cm from the carotid bifurcation. At this distance of the bifurcation the vessels maintained a minimum uniform diameter (Oates et al., 2008). Since the orientation of the carotid arteries may vary from one participant to the other, angle correction or failing this, manual angling of the transducer was used to align the Doppler angle parallel to the vector of blood flow (Bluth et al., 2000). Careful consideration was made to not exceed 60° — as these measurements would be inaccurate. Three distinct pulsed wave spectral tracings containing three consecutive cardiac cycles were recorded.

Spectral Doppler was initiated, 2cm proximal to the carotid bifurcation, to provide a detailed analysis of the distribution of flow in the distal component of the CCAs. The same procedure was carried out 2cm distal to the bifurcation to provide a detailed analysis of the distribution of flow in the proximal component of the ICAs and ECAs. The Spectral Doppler analysis and diameter measurements were repeated three times in the same recording sites of the arteries under the same scan conditions, and the mean of these measurements were used for further analysis.

The Doppler ultrasound series therefore included the following images for each side of each participant:

1. CCA in B mode
2. CCA with Colour & Spectral Doppler
3. ICA origin B mode
4. ICA origin with Colour & Spectral Doppler
5. ECA origin B mode
6. ECA origin with Colour & Spectral Doppler

The diameters, Peak systolic (V_{SYS}), end-diastolic (V_{DIA}) velocities, and Resistance indices[5] (RI) were recorded at each site. The flow waveform was also categorised according to

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[5] An indicator of resistance of an organ to perfusion.

the presence of laminar or turbulent flow. All images were stored on optical disc for off-line analysis with Phillips CX50 Ultrasound system software.

Hemodynamic measures were used to calculate many additional indices. Mean arterial velocity (V_{MEAN}), Pulsitility index and volume flow rate were calculated at each site with the following formulae:

V_{MEAN}:

$$V_{MEAN} = \frac{V_{SYS} + V_{DIA}}{2}$$

Pulsatility index[6] (PI), computed according to the method of Gosling and King (1974):

$$PI = \frac{V_{SYS} - V_{DIA}}{V_{MEAN}}$$

Volume flow rate:

$$Volume\ flow\ rate = V_{SYS} \times\ Cross\ sectional\ area$$

Blood pressure. BP was measured in a calm, quiet setting that minimised distractions and also ensured participant confidentiality. The room temperature remained at a comfortable level (20-24°C). The participant sat in a chair, with back supported, feet flat on the floor (legs uncrossed), and external support was provided for the relevant arm so that the BP cuff remained at heart level for the measurement. BP measures were taken on the left and right upper extremities. Participants were also instructed not to talk during each measurement.

Administration of Handedness Inventory. The inventory was conducted according to the participants language preference (English or Afrikaans; Appendix A and B respectively). Each administration of the inventory followed the same procedure. Scores were recorded, an LQ

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[6]A measure of the variability of blood velocity in a vessel.

calculated, and participants were grouped accordingly. Participants were also asked whether they were pressured into changing their handedness at a young age.

Target Test. Target Tests were administered to assess each participant's hand-proficiency. Subjects were required to execute the Target Tests with each hand in a randomised and counterbalanced order. The Target Speed Test (Appendix F) was administered prior to the Target Accuracy Test to standardise the effects of practice. For each of the Target Tests a laterality ratio was computed using the following equation:

$$TI = \frac{Right\ hand\ score - Left\ hand\ score}{Right\ hand\ score\ + Left\ hand\ score}$$

The Target index (TI) was used for further analysis since it provides a correction for differences in base performance (Krashen, 1972). For hand speed, positive ratios reflected right-sided dominance and negative ratios reflected left-sided dominance. For hand accuracy the converse is true. Demographic information regarding the age and sex of the participants was also collected.

Target speed. Performance on the Target Speed Test was determined by the number of seconds taken to hit the 2mm centre target in 32 targets, arranged in a 4 X 8 matrix on an A4 sheet of paper (Appendix E). Targets consisted of four evenly spaced concentric circles, the largest 12 mm in diameter. By requiring the subject to hit the 2mm centre of each target in succession, accuracy was held constant while speed was measured. Instructions mimicked those of the original test (Borod et al., 1984).

Target accuracy. The Target Accuracy Test used a separate copy of the same matrix used in the Target Speed Test. Scores on this test were determined by the number of points obtained while aiming for the centre of each of the 32 targets. Speed was held constant by requiring subjects to strike the targets in time with a metronome set at 144bmp.

Points were allocated by the location of each mark, with a score range for each target from 0 (outside the 12mm target) to 8 (centre target), providing a score range from 0 to 256 (Figure 3.2). In cases where a line occurred instead of a point, the midpoint of the line was scored. Instructions mimicked those of the original test (Borod et al., 1984).

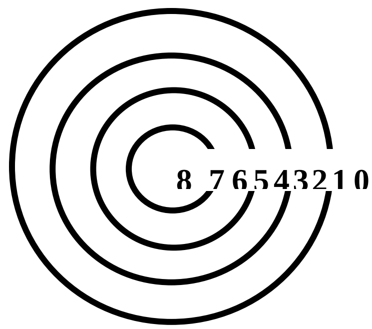

Figure 3.2. Scoring criteria for the Target Accuracy Test

Statistical Analysis

Data was analysed using the IBM SPSS Statistics (version 22) software. Frequency tables and box-and-whisker plots were created in order to better understand the distribution of the data (William, 1980).

One-tailed paired t-tests were used to compare the differences between the left and right arterial geometric parameters of the handedness groups, as classified by their LQ. Normality tests, namely the Shapiro-Wilk, Kolmogrov-Smirnov, and Lillifors were run on each data set. All assumptions of the t-test were upheld. Sample specific descriptive statistics of age, sex, and handedness were also included.

The main data analysis consisted of a series of mixed-design ANOVAs in order to assess interactions between arterial hemodynamics and handedness. For each analysis, the within-subjects factor was the respective arterial hemodynamic parameter (of the left and right carotid arteries) and the between-subjects factor was the participant's handedness (left-handed, right-handed, and ambidextrous). The analysis was conducted for CCAs, ICAs and ECAs. Tests of normality and homoscedasticity (namely Levene's test of equality of variance and Box's test of equality of covariance matrices) were run on each dataset. All assumptions of the mixed-design ANOVA were upheld. Pairwise Bonferroni post-hoc tests were run to identify significant differences within each significant interaction effect.

A discriminant function analysis was used to determine the accurate classification of handedness based on arterial blood volume flow rates of the CCAs and ICAs. Significant predictor variables of handedness were therefore statistically identified (Cooley & Lohnes, 1971). The independent variables of this analysis were the hemodynamic predictors and the dependent variables were the handedness groups, as determined by the participants LQ. Prior to analysis, the predictor variables were inspected to ensure that the assumptions for the analysis were upheld (Klecka, 1980).

The following predictor variables were used in the analysis: X1 = LCCA volume flow rate, X2 = RCCA volume flow rate, X3 = LICA volume flow rate, X4 = RICA volume flow rate. The significance of the discriminant function analysis was determined by an *F*-test, with a 95% confidence level, $p < .05$. Ambidextrous participants were removed from the analysis due to the small sample size ($n = 6$).

Two simple hierarchical multiple regression analyses were conducted on the data, based on variables supported by existing theory, to evaluate how well the hemodynamic volume flow rates predict degree of hand-proficiency — as determined by the speed and accuracy TIs of the participants. The following hierarchical sequence was used:

Step 1: RICA volume flow rate and LICA volume flow rate

Step 2: RCCA volume flow rate and LCCA volume flow rate

Bivariate correlation matrices (Pearson’s and Spearman’s) illustrated the relationship between each predictor variable and the hand-proficiency scores (namely speed and accuracy TIs). All assumptions of the analysis were upheld. Scatterplots were used to visually illustrate the trends in the data.

Cohen’s (1992) rule of thumb for effect size interpretations were used for within-group and between-group comparisons: $d = .10$ (small effect), $d = .30$ (medium effect), and $d = .50$ (large effect). Results of all analyses were considered significant when the p value was less than .05.

Ethical Considerations

The study followed the guidelines for research with human subjects as outlined by the University of Cape Town as well as ethical standards as stipulated by the Health Professions Council of South Africa, and the latest version of the Declaration of Helsinki. Ethical approval from the University of Cape Town Psychology Department as well as from the University of Cape Town’s Faculty of Health Science Research Ethics Committees was obtained. Informed consent was obtained from each participant prior to participation (Appendix G). There were no paediatric cases in this study.

Information acquired from the analysis was used solely for the study, and was kept confidential. The participants were informed of the purpose of the research, and assured that their involvement was voluntary and that they could withdraw from the study at any stage without negative repercussions. There were no overt risks to the participants. Participants were compensated with R50.00 for their participation in the study.Participants were informed that in the event of the discovery of a previously undetected anatomical abnormality during the Doppler ultrasound assessment, confidentiality may be broken, and a medical professional would contact the participant, and discuss possible treatments. Debriefing was offered to all participants.

Results

Results for Chapter 3 are presented in seven sections. The first four sections involve the direct analysis of handedness-related hemodynamic asymmetries and are separated according to the different variables measured. This includes: (i) sex differences, (ii) blood pressure differences, and hemodynamic differences of the (iii) CCA, (iv) ICA, and (v) ECA. The arterial-specific sections (iii - v) include evaluations of arterial diameters, velocities, RI, PI, and volume flow rates. For brevity V_{SYS} and V_{DIA} data points for each artery are omitted from the tables, but they were used to calculate mean blood flow velocity (V_{MEAN}). The last two sections involve (vi) a discriminant function analysis assessing the accuracy to which handedness can be classified according to arterial blood volume flow rates, and (vii) hierarchical multiple regression analyses to evaluate how well the hemodynamic volume flow rates predict degree of hand-proficiency.

Of the 234 participants, 174 were right-handed (74.34%), 54 were left-handed (23.08%) and 6 were Ambidextrous (2.56%; Table 3.1). Only one individual reported social pressure to change their hand dominance and was removed from the study. Doppler ultrasound B-mode, Colour, and Spectral Doppler ultrasound imaging of one right-handed and one left-handed participant visually illustrate the diameter and hemodynamic variability of the left and right carotid arteries (Figure 3.3).

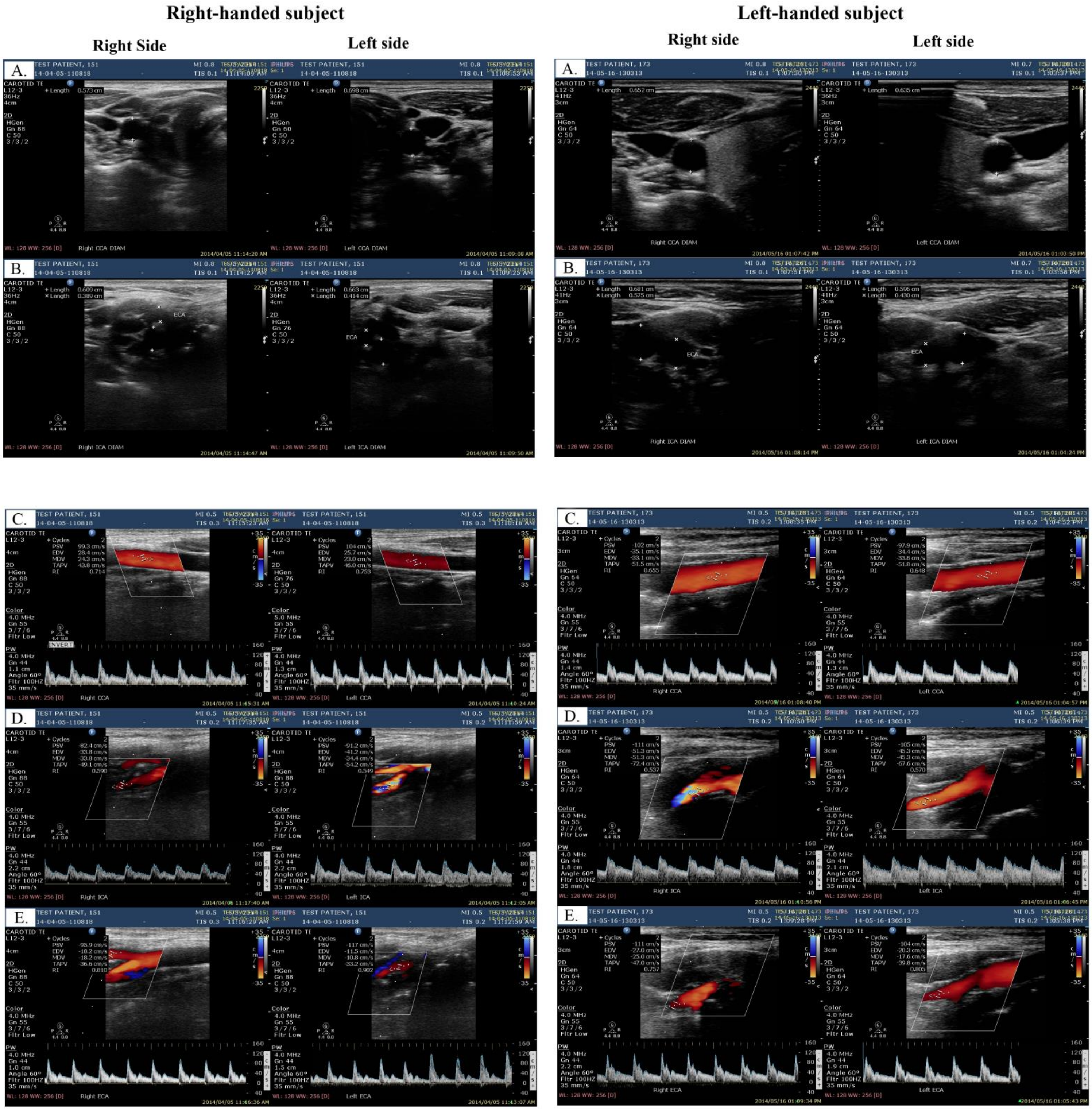

Figure 3.3. Doppler ultrasound B-mode images showing diameters of the CCAs (A), ICAs and ECAs (B); and Colour and Spectral Doppler ultrasound imaging of the CCAs (C), ICAs (D) and ECAs (E) of a right- and left-handed subject.

Sex Differences

Significant sex differences were found in the majority of hemodynamic variables. Overall systolic BP ($F(1, 232)= 55.47$, $p < .001$, $\eta p^2 = .193$) as well as diastolic BP ($F(1, 232)= 8.42$, $p = .004$, $\eta p^2 = .035$) was significantly lower in females than in males. As a consequence to consistently smaller arterial diameters, lower RI and PI, females had significantly lower flow volume rates in the CCAs (Female $M = 33.80 cm^3.s^{-1}$, SD = 0.64; Male $M = 46.07 cm^3.s^{-1}$, $SD = 0.87$; $F(1, 232)= 129.12$, $p < .001$, $\eta p^2 = .358$), ICAs (Female $M = 30.15 cm^3.s^{-1}$, SD = 0.76; Male $M = 37.47 cm^3.s^{-1}$, $SD = 1.05$; $F(1, 232)= 31.92$, $p < .001$, ηp2 = .121) and ECAs (Female $M = 13.57 cm^3.s^{-1}$, SD = 0.54; Male $M = 20.61 cm^3.s^{-1}$, $SD = 0.39$; $F(1, 232)= 113.14$, $p < .001$, $\eta p^2 = .328$). Despite significant differences in V_{MEAN} in the CCAs ($F(1, 232)= 42.88$, $p < .001$, $\eta p^2 = .156$) and ECAs ($F(1, 232)= 35.25$, $p < .001$, $\eta p^2 = .132$) — with significantly lower velocities in females, there were, no significant sex-differences in V_{MEAN} in the ICAs ($F(1, 232)= 0.39$, $p = 0.535$).

Blood Pressure

In right-handers, systolic BP in the right arm (M = 114.23mmHg; SD = 16.02) was significantly higher than the left arm (M = 117.02mmHg; SD = 17.67), $t(173)= -3.16$, $p =.001$, $d= 0.17$. However, the converse was true for diastolic BP — with a higher overall diastolic BP in the left arm (Left M = 69.24mmHg; SD = 10.05; Right M = 67.91mmHg; SD = 10.22), $t(173)= -2.27$, $p = .012$, $d = 0.13$ (Table 3.2). Side-to-side differences in left-handers and ambidextrous participants were negligible.

There were no significant main effects or handedness interactions between the systolic BPs of the different handedness groups (Table 3.3 and Figure 3.4). Although there were no significant main effects for diastolic BP, a significant main effect for handedness was found, *F*(2, 231)= 4.46, *p* = .013; ηp^2 = .037. However, a post-hoc analysis failed to identify which handedness groups were significantly different, possibly due to the small sample size of the ambidextrous group.

There were no significant interaction effects between handedness groups and diastolic BP, *F*(2, 231)= 0.18, *p* = .832 (Figure 3.4). However, Pairwise Bonferroni post-hoc tests showed a significant difference between left diastolic BPs of right-handers and ambidextrous participants, *p* = .023, with a significantly larger diastolic BP in the ambidextrous group (Figure 3.4). Further differences were found between right diastolic BPs of right- and left-handers, *p* = .038, with a significantly larger diastolic BP in left-handers (Figure 3.4).

Table 3.2

Descriptive statistics and one-tailed paired t-tests comparisons of BPs between left and right arms across handedness groups

		Right-handed M (*SD*)	Left-handed M (*SD*)	Ambidextrous M (*SD*)	Total M (*SD*)
Systolic BP (mmHg)	Left arm	114.23 (16.02)	116.93 (13.81)	116.50 (15.44)	114.91 (15.50)
	Right arm	117.02 (17.67)	118.28 (13.72)	116.67 (10.35)	117.30 (16.65)
	p	.001*	.102	.479	-
Diastolic BP (mmHg)	Left arm	69.24 (10.05)	72.28 (9.90)	78.83 (12.35)	70.18 (10.20)
	Right arm	67.91 (10.22)	71.26 (10.63)	75.83 (9.72)	68.89 (10.42)
	p	.012*	.170	.151	-

Note. *p* < .05

Table 3.3

Effects of handedness on Blood pressures of the left and right arms

	Source	*df*	*F*	*p*	ηp^2
Systolic BP	Systolic BP	1	0.84	.361	.004
	Handedness	2	0.35	.704	.003
	Systolic BP*Handedness	2	0.50	.609	.004
Diastolic BP	Diastolic BP	1	2.54	.113	.011
	Handedness	2	4.46	.013*	.037
	Diastolic BP*Handedness	2	0.18	.832	.002

Note. $p < .05$

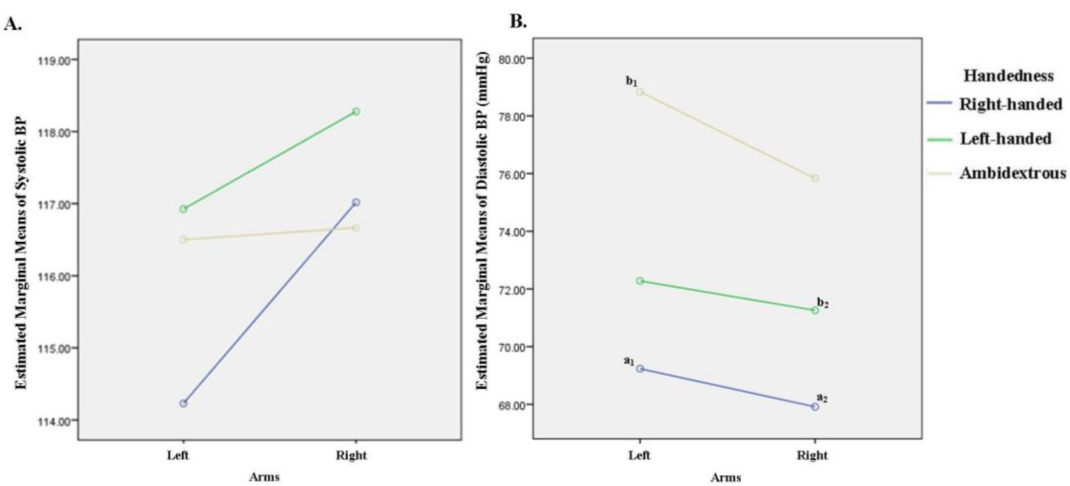

Figure 3.4. Interaction effects of systolic BP (A) and diastolic BP (B) and handedness. Pairwise Bonferroni post-hoc test significance indicated by [ab]

Common Carotid Arteries

Diameter. In right-handers, lumen diameter was significantly larger on the left side (*M* = 6.76mm; *SD* = 0.64) than that on the right (*M* = 6.64mm; *SD* = 0.61), *t*(173)= 2.65, *p* = .005, *d* = 0.19, and the converse was seen in left-handers (LCCA *M* = 6.54mm; *SD* = 0.08; RCCA *M* = 6.83mm; *SD* = 0.07), *t*(53)= -3.52, *p* < .001, *d* = 0.41 (Table 3.4). Side-to-side differences in ambidextrous participants were negligible.

No significant main effects for CCA diameters, $F(1, 231) = 0.11$, $p = .744$, or for handedness, $F(2, 231) = 0.91$, $p = .404$, were found (Table 3.4). However, there was a significant interaction effect between lumen diameter and handedness, $F(2, 231) = 9.01$, $p < .001$, $\eta p^2 = .072$ (Table 3.5). This disordinal interaction is illustrated in Figure 3.5 and shows that differences between the diameters differed significantly between handedness groups. A Pairwise Bonferroni post-hoc test showed a significant difference between LCCA diameters of left- and right-handers in this handedness interaction, $p = .031$(Figure 3.5), with a significantly larger LCCA diameter in the right-handed group.

Table 3.4

Descriptive statistics and one-tailed paired t-tests comparisons of hemodynamic parameters between LCCA and RCCA across handedness groups

	Arteries	Right-handed M (*SD*)	Left-handed M (*SD*)	Ambidextrous M (*SD*)	Total M (*SD*)
Diameter (mm)	LCCA	6.76 (0.64)	6.54 (0.75)	7.05 (0.71)	6.72 (0.68)
	RCCA	6.64 (0.61)	6.83 (0.71)	6.98 (1.03)	6.69 (0.65)
	p	.005*	.000*	.390	-
V_{MEAN} ($cm.s^{-1}$)	LCCA	71.97 (11.53)	70.91 (12.58)	69.66 (17.07)	71.67 (11.88)
	RCCA	63.86 (11.97)	68.79 (12.78)	57.78 (11.04)	64.84 (12.31)
	p	.000*	.088	.032*	-
RI	LCCA	.721 (.060)	.727 (.057)	.680 (.063)	.721 (.059)
	RCCA	.708 (.056)	.710 (.058)	.687 (.075)	.708 (.057)
	p	.000*	.019*	.369	-
PI	LCCA	1.16 (0.15)	1.15 (0.13)	1.04 (0.14)	1.14 (0.14)
	RCCA	1.10 (0.14)	1.11 (0.14)	1.06 (0.17)	1.10 (0.14)
	p	.000*	.020*	.359	-
Volume flow rate ($cm^3.s^{-1}$)	LCCA	41.23 (12.33)	37.85 (10.87)	41.89 (13.24)	40.46 (12.07)
	RCCA	34.47 (9.01)	39.57 (11.26)	33.89 (9.37)	35.63 (9.78)
	p	.000*	.065	.005*	-

Note. $p < .05$

Table 3.5

Effects of handedness on hemodynamic parameters of the CCAs

	Source	*df*	*F*	*p*	ηp^2
Diameter	Diameter	1	0.11	.744	.000
	Handedness	2	0.91	.404	.008
	Diameter*Handedness	2	9.01	.000*	.072
V_{MEAN}	V_{MEAN}	1	22.19	.000*	.088
	Handedness	2	1.21	.300	.010
	V_{MEAN}*Handedness	2	7.12	.001*	.058
RI	RI	1	0.94	.333	.004
	Handedness	2	1.25	.289	.011
	RI*Handedness	2	0.63	.536	.005
PI	PI	1	0.95	.331	.004
	Handedness	2	1.33	.268	.011
	PI*Handedness	2	0.58	.563	.005
Volume flow rate	Volume flow rate	1	10.16	.002*	.042
	Handedness	2	0.16	.850	.001
	Volume flow rate*Handedness	2	17.22	.000*	.130

Note. $p < .05$

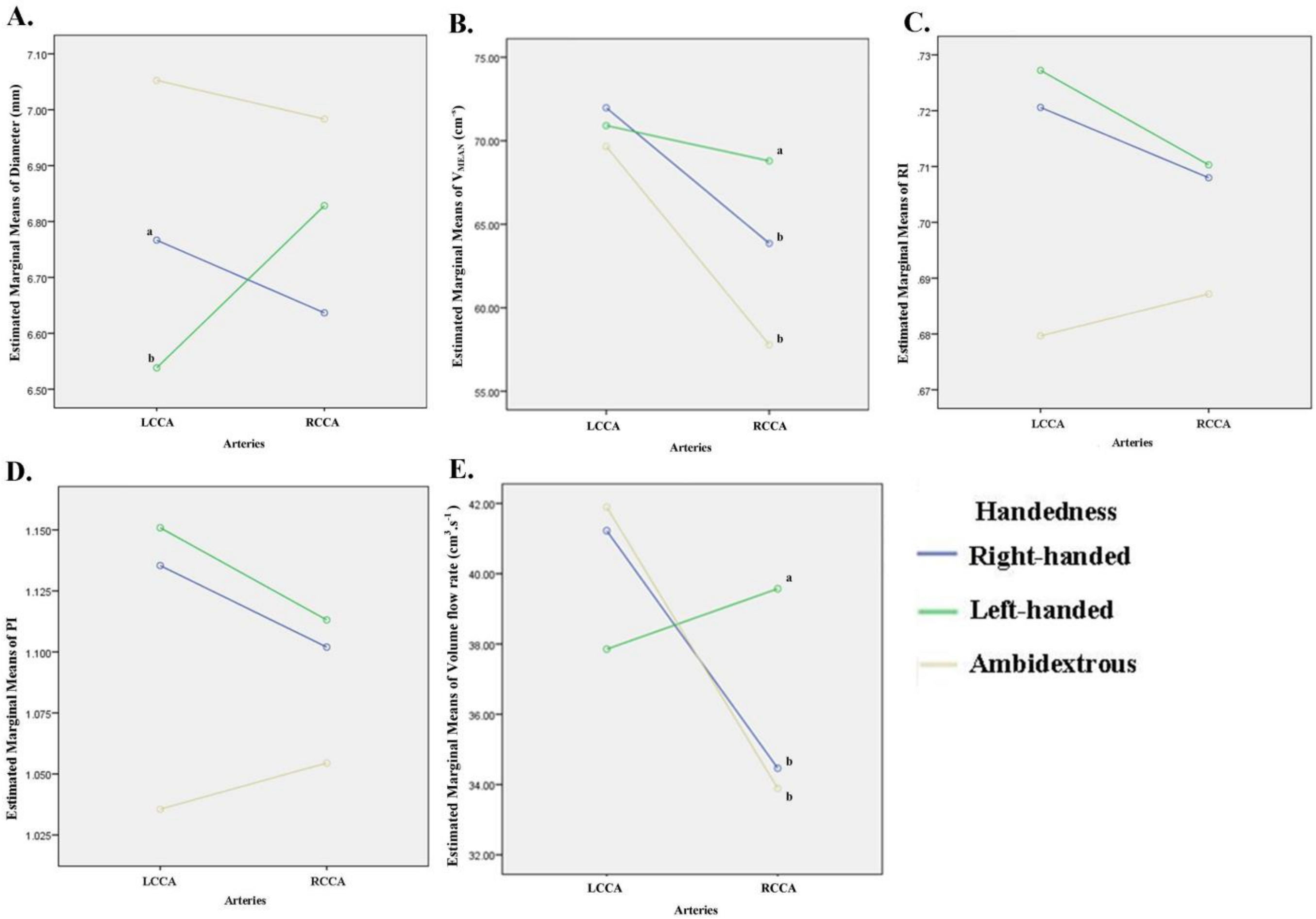

Figure 3.5. Interaction effects of CCA diameters (A), V_{MEAN} (B), RI (C), PI(D), Volume flow rate (E) and handedness. Pairwise Bonferroni post-hoc test significance indicated by [ab]

Mean flow velocity. In right-handers V_{MEAN} was significantly higher on the left-side (M = 71.97cm.s^{-1}; SD = 11.53) than on the right (M = 63.86cm.s^{-1}; SD = 11.97), $t(173)$= 10.18, $p <$ .001, d = 0.69 (Table 3.4). The same was true for ambidextrous participants (LCCA M = 69.66 cm.s^{-1}; SD = 17.07; RCCA M = 57.78cm.s^{-1}; SD = 11.04), $t(5)$= 2.38, p = .032, d = 2.12. Side-to-side V_{MEAN} differences were negligible in left-handers.

A significant main effect for CCA V_{MEAN} — with a higher overall velocity on the left side in all participants was found, $F(1, 231)= 22.29$, $p < .001$, $\eta p^2 = .088$ (Table 3.5). There was no significant main effect for handedness, $F(2, 231)= 1.21$, $p =.30$.

There was, however, a significant interaction effect between V_{MEAN} and handedness, $F(2, 231)= 7.12$, $p = .001$, $\eta p^2 = .058$ (Table 3.5). Therefore, differences in V_{MEAN} differed significantly between the handedness groups. This disordinal interaction is illustrated in Figure 3.5. A Pairwise Bonferroni post-hoc test showed a significant difference in RCCA V_{MEAN} between left- and right-handers in this handedness interaction, $p = .010$, as well as between left-handers and ambidextrous groups $p = .036$ (Figure 3.5), with a significantly faster V_{MEAN} on the right side in left-handers in both instances.

Resistance and Pulsitility indices. In right-handers, RI was significantly greater on the left side ($M = .721$; $SD = .06$) than on the right ($M = .708$; $SD = .056$), $t(173)= 3.33$, $p < .001$, $d = 0.22$. The same was true for left-handers (LCCA $M = .727$; $SD = .057$; RCCA $M = .710$; $SD = .058$), $t(53)= 2.13$, $p = .019$, $d = 0.30$ (Table 3.4). Side-to-side differences in ambidextrous participants were negligible. There were no significant main effects or handedness interactions between the RI of the CCA arteries of the different handedness groups (Table 3.5 and Figure 3.5).

In right-handers, PI was significantly greater on the left side ($M = 1.14$; $SD = 0.15$) than on the right ($M = 1.10$; $SD = 0.14$), $t(173)= 3.67$, $p < .001$, $d = 0.24$. The same was true for left-handers (LCCA $M = 1.15$; $SD = 0.13$; RCCA $M = 1.11$; $SD = 0.14$), $t(53)= 2.11$, $p = .020$, $d = 0.28$ (Table 3.4). Side-to-side differences in ambidextrous participants were negligible. There were no significant main effects or handedness interactions between the PI of the CCA arteries of the different handedness groups (Table 3.5 and Figure 3.5).

Volume flow rate. In right-handers, volume flow rate was significantly higher on the left side (*M* = 41.22cm^3.s^{-1}; *SD* = 12.33) than on the right (*M* = 34.47cm^3.s^{-1}; *SD* = 11.26), *t*(173)= 9.10, *p* < .001, *d* = 0.63). The same was true for the ambidextrous group (LCCA *M* = 41.90cm^3.s^{-1}; *SD* = 12.07; RCCA *M* = 33.89cm^3.s^{-1}; *SD* =9.37), *t*(53)= 4.11, *p* = .005, *d* = 0.70 (Table 3.4). Although higher on the right side, side-to-side differences in left-handers were not significant.

A significant main effect for CCA volume flow rate — with a higher overall flow rate on the left side in all participants was found, *F*(1, 231)= 10.16, *p* = .002, ηp^2 = .042 (Table 3.5). There was no significant main effect for handedness, *F*(2, 231)= 0.16, *p* =.850.

There was, however, a significant interaction effect between volume flow rate and handedness, *F*(2, 231)= 17.22, *p* < .001, ηp^2 = .130 (Table 3.5). This disordinal interaction is illustrated in Figure 3.5. A Pairwise Bonferroni post-hoc test showed a significant difference in RCCA volume flow rate between left- and right-handers in this handedness interaction, *p* = .001 (Figure 3.5), with significantly higher flow rates on the right side in left-handers in both instances.

Internal Carotid Arteries

Diameter. In accordance with asymmetries found in the CCAs, in right-handers, lumen diameter was significantly larger on the left side (*M* = 6.82mm; *SD* = 0.96) than on the right (*M* = 6.29mm; *SD* = 0.96), *t*(173)= 8.63, *p* < .001, *d* = 0.57. The converse was seen in left-handers (LICA *M* = 6.52mm; *SD* = 1.02; RICA *M* = 6.81mm; *SD* = 0.95), *t*(53)= -3.06, *p* = .002, *d* = 0.29 (Table 3.6). Side-to-side differences in ambidextrous participants were negligible.

No significant main effects for ICA diameters, *F*(1, 231)= 0.39, *p* = .531, ηp^2 = .002, or for handedness, *F*(2, 231)= 0.64, *p* = .529, were found (Table 3.7). However, there was a significant interaction effect between lumen diameter of the ICAs and handedness, *F*(2, 231)= 22.87, *p* <

.001, $\eta p^2 = .165$ (Table 3.7). This disordinal interaction is illustrated in Figure 3.6 and shows that differences between the diameters differed significantly between handedness groups. A Pairwise Bonferroni post-hoc test showed a significant difference between RICA diameters of left- and right-handers in this handedness interaction, $p < .001$ (Figure 3.6), with a significantly larger diameter on the right side left-handers. These findings are in accordance with handedness interactions identified in the CCAs.

Table 3.6

Descriptive statistics and one-tailed paired t-tests comparisons of hemodynamic parameters between LICA and RICA across handedness groups

	Arteries	Right-handed M (*SD*)	Left-handed M (*SD*)	Ambidextrous M (*SD*)	Total M (*SD*)
Diameter (mm)	LICA	6.82 (0.96)	6.52 (1.02)	6.86 (2.10)	6.75 (1.01)
	RICA	6.29 (0.90)	6.81 (0.95)	6.89 (1.52)	6.43 (0.96)
	p	.000*	.002*	.474	-
V_{MEAN} ($cm.s^{-1}$)	LICA	66.11 (11.81)	66.17 (10.30)	64.53 (12.74)	66.08 (11.46)
	RICA	61.16 (11.56)	70.90 (11.95)	62.69 (20.55)	63.45 (12.55)
	p	.000*	.004*	.386	-
RI	LICA	.628 (.075)	.617 (.067)	.588 (.046)	.624 (.073)
	RICA	.610 (.083)	.601 (.076)	.546 (.127)	.606 (.083)
	p	.004*	.070	.207	-
PI	LICA	0.93 (0.17)	0.90 (0.14)	0.84 (0.09)	0.92 (0.16)
	RICA	0.89 (0.17)	0.88 (0.16)	0.77 (0.25)	0.88 (0.17)
	p	.001*	.244	.359	-
Volume flow rate ($cm^3.s^{-1}$)	LICA	36.05 (12.16)	32.53 (10.51)	32.85 (12.89)	35.16 (11.86)
	RICA	27.90 (9.72)	37.50 (10.95)	31.91 (17.21)	30.21 (10.66)
	p	.024*	.000*	.365	-

Note. $p < .05$

Table 3.7

Effects of handedness on hemodynamic parameters of the ICAs

	Source	*df*	*F*	*p*	ηp^2
Diameter	Diameter	1	0.39	.531	.002
	Handedness	2	0.64	.529	.005
	Diameter*Handedness	2	22.87	.000*	.165
V_{MEAN}	V_{MEAN}	1	0.14	.709	.001
	Handedness	2	5.12	.007*	.042
	V_{MEAN}*Handedness	2	12.15	.000*	.095
RI	RI	1	3.96	.048*	.017
	Handedness	2	2.13	.122	.018
	RI*Handedness	2	0.25	.781	.002
PI	PI	1	2.44	.120	.010
	Handedness	2	1.84	.162	.016
	PI*Handedness	2	0.61	.545	.005
Volume flow rate	Volume flow rate	1	0.10	.319	.004
	Handedness	2	1.91	.151	.016
	Volume flow rate*Handedness	2	40.44	.000*	.259

Note. $p < .05$

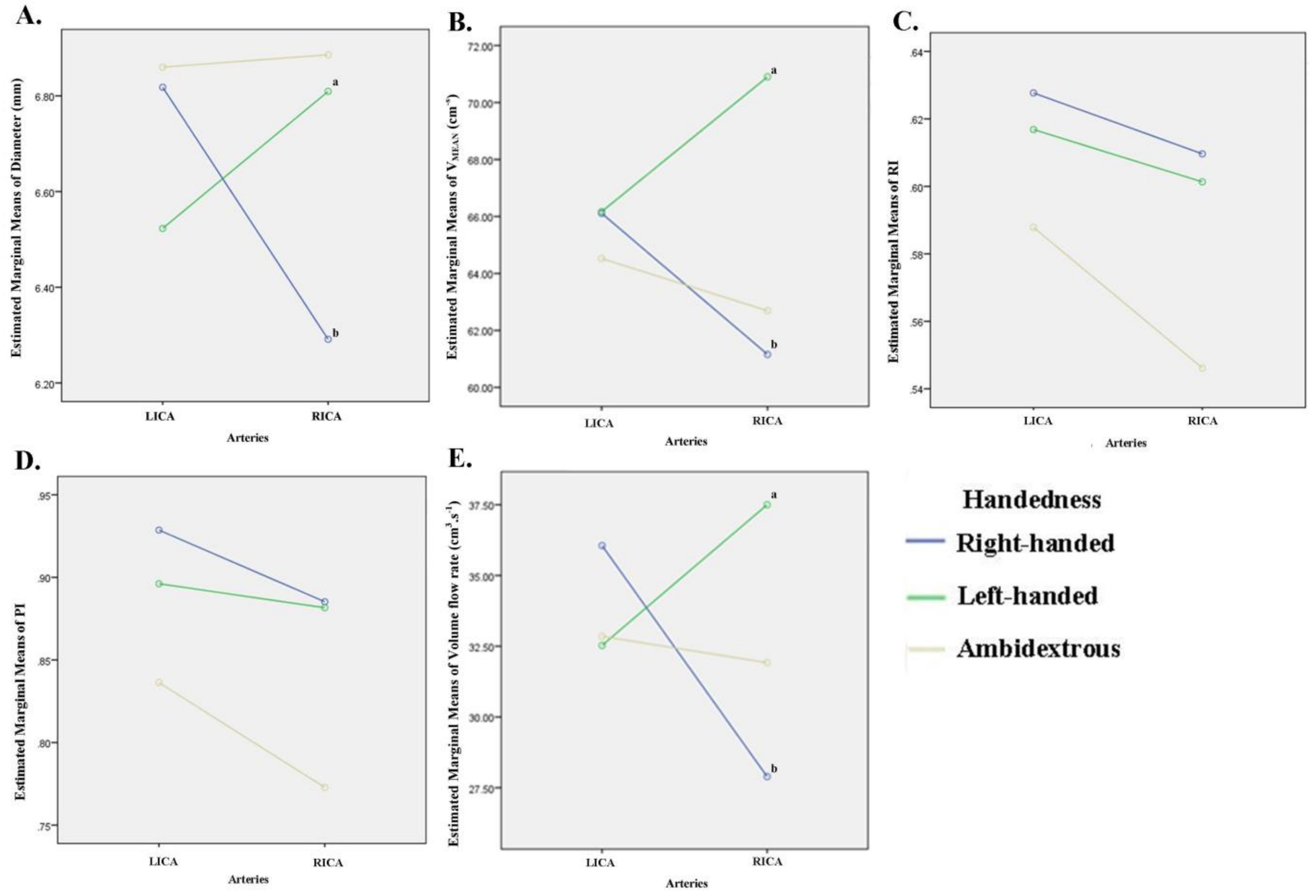

Figure 3.6. Interaction effects of ICA diameters (A), V_{MEAN} (B), RI (C), PI(D), Volume flow rate (E) and handedness. Pairwise Bonferroni post-hoc test significance indicated by [ab]

Mean flow velocity. In right-handers, V_{MEAN} was significantly higher on the left side (M = 66.11cm.s^{-1}; SD = 11.81) than on the right (M = 66.17cm.s^{-1}; SD = 10.3), $t(173)= 5.22$, $p < .001$, d = 0.42. The converse was seen in left-handers (LICA M = 61.16cm.s^{-1}; SD = 11.56; RICA M = 70.90cm.s^{-1}; SD = 11.95), $t(53)= -2.73$, $p = .004$, d = 0.42 (Table 3.6). Side-to-side differences in ambidextrous participants were negligible.

No significant main effect for ICA V_{MEAN} was found, $F(1, 231) = 0.14$, $p = .709$, ηp^2 = .001 (Table 3.7). There was, however, a significant main effect for handedness, $F(2, 231)= 5.12$, $p = .007$, $\eta p^2 = .042$ — where the overall V_{MEAN} (averaged across both arteries) was significantly higher in left-handers (*M* = 68.54) than in right-handers (*M* = 63.64), *p* = .005. There was also a significant interaction effect between V_{MEAN} and handedness, $F(2, 231) = 12.15$, $p < .001$, $\eta p^2 = .095$ (Table 3.7). This disordinal interaction is illustrated in Figure 3.6 and shows that the differences in V_{MEAN} differed significantly between handedness groups. A Pairwise Bonferroni post-hoc test showed a significant difference between RICA V_{MEAN} between left- and right-handers in this handedness interaction, $p < .001$ (Figure 3.6), with a significantly faster RICA V_{MEAN} in left-handers.

Resistance and Pulsitility indices. In right-handers, RI was significantly greater on the left side (*M* =.628; *SD* = .075) than on the right (*M* = .610; *SD* = .083), $t(173) = 2.69$, *p* = .004, *d* = 0.23 (Table 3.6). Side-to-side differences in left-handers and ambidextrous participants were negligible.

A significant main effect for ICA RI — with a higher overall RI on the left side in all participants was found, $F(1, 231) = 3.97$, $p = .048$, $\eta p^2 = .017$ (Table 3.7). There was no significant main effect for handedness or handedness interactions between the RI of the ICA arteries of the different handedness groups (Table 3.7 and Figure 3.6).

Similarly, in right-handers, PI was significantly greater on the left side (*M* = 0.93; *SD* = 0.17) than on the right (*M* = 0.89; *SD* = 0.17), $t(173) = 3.12$, *p* = .001, *d* = 0.24. Side-to-side differences in left-handers and ambidextrous participants were negligible. However, no significant main effects or handedness interactions were found between the PI of the ICAs of the different handedness groups (Figure 3.6).

Volume flow rate. In right-handers, volume flow rate was significantly greater on the left side (*M* = 36.05; *SD* = 12.16) than on the right (*M* = 27.90; *SD* = 9.72), $t(173) = 10.82$, $p < .001$, *d* = 0.74. The converse was seen in left-handers (LICA *M* = 32.53; *SD* = 10.51; RICA *M* = 37.50;

SD = 10.95), *t*(53)= -5.35, $p < .001$, *d* = 0.46 (Table 3.6). Side-to-side differences in ambidextrous participants were negligible.

No significant main effects for ICA volume flow rate, *F*(1, 231)= 1.00, *p* = .319, or for handedness, F(2, 231)= 1.91, *p* =.151, $\eta p^2 = .016$, were found (Table 3.7). There was, however, a significant interaction effect between volume flow rate and handedness, *F*(2, 231) = 40.44, $p < .001$, $\eta p^2 = .259$ (Table 3.7). This disordinal interaction is illustrated in Figure 3.6, and shows that the differences in volume flow rate differed significantly between handedness groups. A Pairwise Bonferroni post-hoc test showed a significant difference in RICA volume flow rate between left- and right-handers within this handedness interaction, $p < .001$ (Figure 3.6), with a significantly greater RICA flow rate in left-handers. These findings are in accordance with handedness interactions identified in the CCAs.

External Carotid Arteries

Diameter. Side-to-side differences in all handedness groups were negligible. Simularly, there were no significant main effects or handedness interactions between the diameters of the ECAs of the different handedness groups (Table 3.8 and 3.9, and Figure 3.7). Pairwise Bonferroni post-hoc tests did, however, show a significant difference between the RECA diameter of right-handers and left-handers, $p < .001$ (Figure 3.7), with a significantly larger RECA diameter in left-handers.

Table 3.8

Descriptive statistics and one-tailed paired t-tests comparisons of hemodynamic parameters between LECA and RECA across handedness groups

	Arteries	Right-handed M (*SD*)	Left-handed M (*SD*)	Ambidextrous M (*SD*)	Total M (*SD*)
Diameter (mm)	LECA	4.58 (0.74)	4.72 (0.82)	4.57 (0.65)	4.61 (0.75)
	RECA	4.56 (0.68)	4.83 (0.82)	4.65 (0.85)	4.62 (0.73)
	p	.307	.176	.351	-
V_{MEAN} ($cm.s^{-1}$)	LECA	55.36 (11.70)	60.48 (13.48)	58.62 (13.27)	56.63 (12.31)
	RECA	52.85 (11.96)	56.29 (11.86)	57.42 (9.55)	53.76 (11.94)
	p	.002*	.006*	.340	-
RI	LECA	.811 (.056)	.823 (.048)	.759 (.063)	.812 (.055)
	RECA	.803 (.063)	.815 (.047)	.779 (.065)	.805 (.060)
	p	.022*	.134	.104	-
PI	LECA	1.36 (0.16)	1.40 (0.14)	1.23 (0.17)	1.37 (0.15)
	RECA	1.34 (0.18)	1.38 (0.13)	1.28 (0.17)	1.35 (0.17)
	p	.032*	.132	.108	-
Volume flow rate ($cm^3.s^{-1}$)	LECA	15.74 (6.07)	18.59 (8.33)	16.38 (8.00)	16.41 (6.79)
	RECA	14.85 (6.33)	17.84 (6.71)	16.90 (8.47)	15.59 (6.57)
	p	.024*	.252	.365	-

Note. $p < .05$

Table 3.9

Effects of handedness on hemodynamic parameters of the ECAs

	Source	*df*	*F*	*p*	ηp^2
Diameter	Diameter	1	0.26	.608	.001
	Handedness	2	1.91	.151	.016
	Diameter*Handedness	2	0.77	.466	.007
V_{MEAN}	V_{MEAN}	1	2.74	.099	.012
	Handedness	2	3.50	.032*	.029
	V_{MEAN}*Handedness	2	0.56	.571	.005
RI	RI	1	0.03	.863	.000
	Handedness	2	3.03	.050*	.026
	RI*Handedness	2	0.85	.430	.007
PI	PI	1	0.02	.893	.000
	Handedness	2	3.19	.043*	.027
	PI*Handedness	2	0.74	.479	.006
Volume flow rate	Volume flow rate	1	0.16	.692	.001
	Handedness	2	5.33	.005*	.044
	Volume flow rate*Handedness	2	0.15	.865	.001

Note. $p < .05$

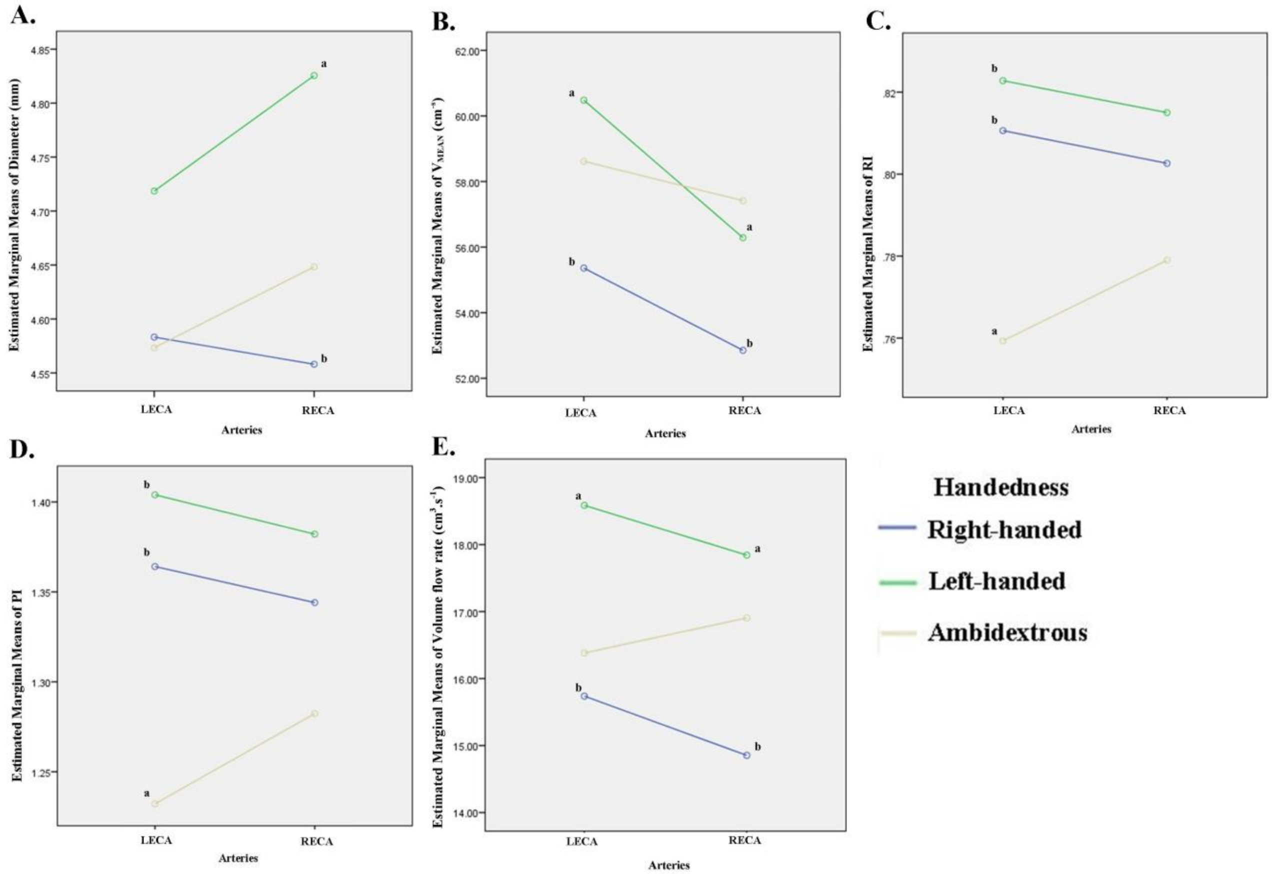

Figure 3.7. Interaction effects of ECA diameters (A), V_{MEAN} (B), RI (C), PI(D), Volume flow rate (E) and handedness. Pairwise Bonferroni post-hoc test significance indicated by [ab]

Mean flow velocity. In right-handers, V_{MEAN} was significantly greater on the left side (M = 55.36cm.s^{-1}; SD = 11.70) than on the right (M = 52.85cm.s^{-1}; SD = 11.96), $t(173)= 3.07$, p = .002, d = 0.21. The same was true for left-handers (LECA M = 60.48cm.s^{-1}; SD = 13.48; RECA M = 56.29cm.s^{-1}; SD = 11.86), $t(53)= 2.64$, p = .006, d = 0.33 (Table 3.8). Side-to-side differences in ambidextrous participants were negligible.

No significant main effect for ECA V_{MEAN} was found, $F(1, 231)= 2.74$, p = .099 (Table 3.9). There was, however, a significant main effect for handedness, $F(2, 231)= 3.50$, p = .032; ηp^2 = .029 — where overall V_{MEAN} (across both arteries) were significantly higher in right-handers (*M* = 54.11) than in left-handers (*M* = 58.38), *p* = .033. There was no significant interaction effect between ECA V_{MEAN} and handedness groups, *F*(2, 231)= 0.56, *p* = .571. However, Pairwise Bonferroni post-hoc tests showed a significant difference between LECA and RECA mean velocities of right-handers and left-handers, *p* = .007 and *p* < .001 respectively (Figure 3.7), with a significantly faster V_{MEAN} in both arteries in left-handers.

Resistance and Pulsitility indices. In right-handers, RI was significantly greater on the left side (*M* = .811; *SD* = .056) than on the right (*M* = .803; *SD* = .063), *t*(173)= 2.03, *p* = .022, *d* = 0.13 (Table 3.8). Side-to-side differences in left-handers and ambidextrous participants were negligible.

No significant main effect for ECA RI was found, *F*(1, 231) = 0.03, *p* = .863 (Table 3.9). Although a significant main effect for handedness was found, *F*(2, 231)= 3.03, *p* = .050; ηp^2 = .026, a post-hoc analysis failed to identify which handedness groups were significantly different, possibly due to the small sample size of the ambidextrous group. There was no significant interaction effect between ECA RI and handedness groups, *F*(2, 231)= 0.85, *p*=.430 (Figure 3.7). However, Pairwise Bonferroni post-hoc tests showed a significant difference in LECA RI between right-handers and ambidextrous participants, *p* = .024 (Figure 3.7), and left-handers and ambidextrous participants, *p* = .007, with a significantly smaller LECA RI in ambidextrous participants in both instances.

In right-handers, PI was significantly greater on the left side (*M* = 1.36; *SD* = 0.16) than on the right (*M* = 1.34; *SD* = 0.18), *t*(5)= -1.42, *p* = .032, *d* = 1.27 (Table 3.8). Side-to-side differences in left-handers and ambidextrous participants were negligible.

No significant main effect for ECA PI was found, *F*(1, 231)= 0.02, *p* = .893 (Table 3.9). There was, however, a significant main effect for handedness, *F*(2, 231)= 3.19, *p* = .043; ηp^2 = .027 — where overall PI (across both arteries) was significantly higher in left-handers (*M* =

1.39) than in the ambidextrous groups (*M* = 1.26), $p = .018$ (Table 3.9). There was no significant interaction effect between ECA PI and handedness groups, $F(2, 231) = 0.74$, $p = .479$. However, Pairwise Bonferroni post-hoc tests showed a significant difference in LECA PI between right-handers and ambidextrous participants, $p = .036$ (Figure 3.7), and left-handers and ambidextrous participants, $p = .009$, with a significantly smaller LECA PI in ambidextrous participants in both instances.

Volume flow rate. In right-handers, volume flow rate was significantly greater on the left side (*M* = 15.74$cm^3.s^{-1}$; *SD* = 6.07) than on the right (*M* = 14.85$cm^3.s^{-1}$; *SD* = 6.33), $t(173) = 2.01$, $p = .047$, $d = 0.14$ (Table 3.8). Side-to-side differences in left-handed and ambidextrous participants were negligible.

No significant main effects for ECA volume flow rate or handedness interactions between the volume flow rates of the different handedness groups were found (Table 3.9). There was, however, a significant main effect for handedness, $F(2, 231) = 5.33$, $p = .005$; $\eta p^2 = .044$ — where overall flow rates (across both arteries) was significantly higher in left-handers (*M* = 18.21$cm^3.s^{-1}$) than in right-handers (*M* = 15.30$cm^3.s^{-1}$), $p = .004$.

Pairwise Bonferroni post-hoc tests showed a significant difference in both LECA and RECA volume flow rates between right-handers and left-handers, $p = .007$ and $p < .001$ respectively (Figure 3.7), with significantly greater volume flow rates in both arteries of left-handers than in right-handers.

Discriminant Function Analysis

A discriminant function analysis was conducted to assess whether arterial blood volume flow rates could accurately classify an individual's handedness (i.e. right-handed or left-handed). The resulting discriminant analysis significantly differentiated the handedness groups, $\Lambda = .669$,

χ^2 (4) = 90.06, *p* < .001. Tests of equality of group means and an evaluation of the structure matrix revealed only two significant predictors, namely volume flow rate in the RICA (.581) and RCCA (.323), with volumes in the LICA, LCCA as poor predictors (Table 3.10). Therefore, the variability of the arteries feeding the right hemisphere significantly differentiates the handedness groups. The cross-validated classification showed that overall 84.2% of cases were correctly classified — with accurate group membership predictions for 93.7% of right-handers and 53.7% of left-handers (Table 3.11)

The following discriminant equation results:

D = (-.035 × LCCA Volume flow rate) + (.047 × RCCA Volume flow rate) + (-.074 × LICA Volume flow rate) + (.107 × RICA Volume flow rate) -.930

Table 3.10.

Tests of equality of group means and structure matrix of rate contribution to the model

	Function	Wilks' Lambda	*F*	*df1*	*df2*	*p*
LCCA Volume flow rate	-.170	.986	3.24	1	226	.073
RCCA Volume flow rate	.323	.951	11.70	1	226	.001*
LICA Volume flow rate	-.181	.984	3.68	1	226	.056
RICA Volume flow rate	.581	.857	37.80	1	226	.000*

Table 3.11.

Volume flow rate classification table

			Predicted group membership		
		Handedness	Right-handed	Left-handed	Total
Original[a]	Count	Right-handed	163	11	174
		Left-handed	25	29	54
	%	Right-handed	93.1	6.3	100
		Left-handed	46.3	53.7	100
Cross-validated[b,c]	Count	Right-handed	163	11	174
		Left-handed	25	29	54
	%	Right-handed	93.1	6.3	100
		Left-handed	46.3	53.7	100

[a] 84.2% of original grouped cases correctly classified.
[b] Cross validation is done only for those cases in the analysis. In cross validation, each case is classified by the functions derived from all cases other than that case.
[c] 84.2% of cross-validated grouped cases correctly classified.

Volume Flow Rate Prediction of Hand-proficiency

Two linear multiple regression analyses were conducted to evaluate how well the hemodynamic volume flow rates of the ICAs and CCAs predict degree of hand-proficiency — as derived from TIs of speed and accuracy Target Tests.

The following hierarchical sequence was used for each analysis:

Step 1: RICA volume flow rate and LICA volume flow rate

Step 2: RCCA volume flow rate and LCCA volume flow rate

Speed Target Index. All variables were kept in the regression model as the change in R^2 was significant (Table 3.12). At step 1, ICA volume flow rates significantly predicted speed hand-proficiency ($R^2 = .253$, $F(2, 225) = 38.17$, $p < .001$), explaining 25.3% of the variance in hand speed (Table 3.12). At step 2, CCA volume flow rates significantly contributed to the model ($R^2 = .294$, $F(1, 223) = 6.37$, $p = .002$), explaining another 4% of the variance.

In the overall model, RICA volume flow rate had the greatest influence on a speed hand-proficiency (β = 0.513; Table 3.13 and Figure 3.8). LICA volume flow rate was the second best predictor (β = -.279). This is further validated by the non-overlapping confidence intervals demonstrated in Table 3.13.

While volume flow rates in the right ICA and CCA were positively correlated with hand speed proficiency, left ICA and CCA were negatively correlated with hand speed proficiency. Therefore the direction of the coefficients suggests that higher volume flow rates in the arteries feeding the right hemisphere were associated with high speed TI scores (indicative of left-handers). Higher volume flow rates in arteries feeding the left hemisphere were associated with lower speed TI scores (indicative of right-handers). Overall, extracranial carotid volume flow rate explained 29.4% of the variance in hand speed, $F(4, 223) = 23.18$, $p < 0.001$.

Table 3.12.

Regression model summary of ICA and CCA volume flow rates and speed hand-proficiency

						Change statistic		
Model	*R*	R^2	Adjusted R^2	F	*p.*	ΔR^2	ΔF	Sig. F change
1	.503[a]	.253	.247	38.173	.000*	.253	38.17	.000*
2	.542[b]	.294	.281	23.180	.000*	.040	6.37	.002*

Note. p < .05
[a] Predictors: (Constant), RICA volume flow rate, LICA volume flow rate
[b] Predictors: (Constant), RICA volume flow rate, LICA volume flow rate RICA volume flow rate, LICA volume flow rate

Table 3.13.

Regression analysis of ICA and CCA volume flow rate and speed hand-proficiency for the final model

	Unstandardized Coefficients		Standardized Coefficients			95% confidence interval for *B*	
	B	*SEB*	β	*t*	*p.*	Lower Bound	Upper Bound
Constant	-.226	.050	-	-4.49	.000*	-.325	-.127
LICA volume flow rate	-.005	.001	-.279	-3.72	.000*	-.008	-.002
RICA volume flow rate	.010	.001	.513	6.86	.000*	.007	.013
LCCA volume flow rate	-.005	.001	-.264	-3.44	.001*	-.007	-.002
RCCA volume flow rate	.004	.002	.207	2.64	.009*	.001	.008

Note. R^2=.294; p < .001

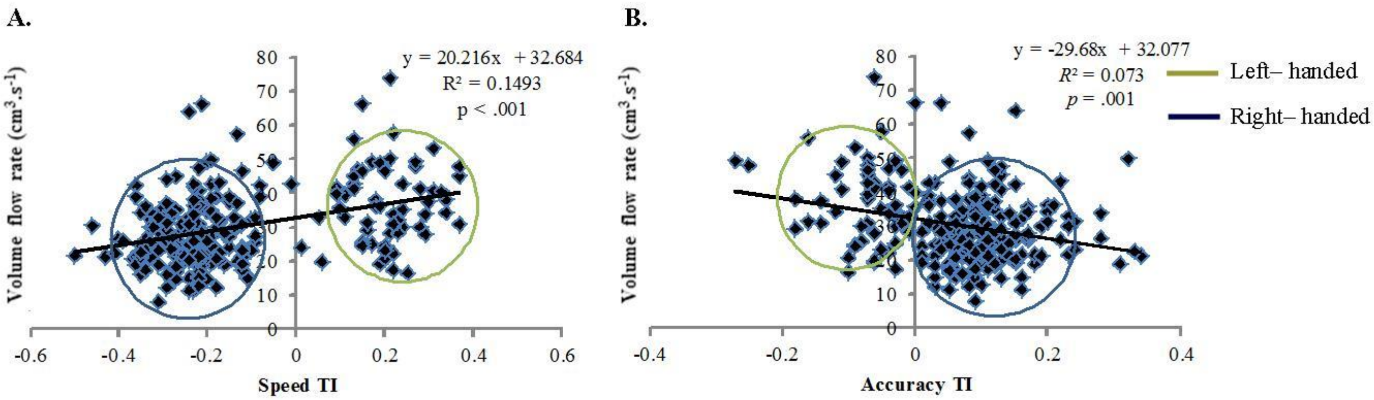

Figure 3.8. Scatterplots of RICA volume flow rate (most significant volume flow rate predictor in both regression models) and hand-proficiency as indicated by Speed TI (A) and Accuracy TI (B). Main left- and right-handed groupings, as classified by participant LQ, are circled accordingly

Accuracy Target Index. All variables were kept in the regression model as the change in R^2 was significant (Table 3.14). At step 1, ICA volume flow rates significantly predict accurate hand-proficiency (R^2 = .153, F(2, 225)= 20.29, p < .001), explaining 15.3% of the variance in hand accuracy (Table 3.14). At step 2, CCA volume flow rates significantly contributed to the model (R^2 = .201, $F(1, 223)$= 6.694, p = .002), explaining another 2% of the variance.

In the overall model, RICA volume flow rates seemed to have the greatest influence on a speed hand-proficiency (β = - 0.359; Table 3.15 and Figure 3.8). LCCA volume flow rate was the second best predictor (β = .283). This is further validated by the non-overlapping confidence intervals demonstrated in Table 3.15.

While volume flow rates in the right ICA and CCA were negatively correlated with hand accuracy proficiency, left ICA and CCA were positively correlated with hand speed proficiency. Therefore, the direction of the coefficients suggests, that higher volume flow rates in the arteries feeding the right hemisphere were associated with low accuracy TIs (indicative of left-handers), whereas higher volume flow rates in arteries feeding the left hemisphere were associated with higher speed TI scores (indicative of right-handers). Overall, extracranial volume flow rate explained 20.1% of the variance in hand accuracy, $F(4, 223)$= 14.00, $p < 0.001$.

Table 3.14.

Regression model summary of ICA and CCA volume flow rates and speed hand-proficiency

						Change statistic		
Model	*R*	R^2	Adjusted R^2	F	*p.*	ΔR^2	ΔF	Sig. F change
1	.391[a]	.153	.145	20.29	.000*	.153	20.29	.000*
2	.448[b]	.201	.186	14.00	.000*	.048	6.69	.002*

Note. $p < .05$
[a] Predictors: (Constant), RICA volume flow rate, LICA volume flow rate
[b] Predictors: (Constant), RICA volume flow rate, LICA volume flow rate RICA volume flow rate, LICA volume flow rate

Table 3.15.

Regression analysis of ICA and CCA volume flow rate and accuracy hand-proficiency for the final model

	Unstandardized Coefficients		Standardized Coefficients			95% confidence interval for *B*	
	B	*SEB*	β	*t*	*p.*	Lower Bound	Upper Bound
Constant	.090	.026	-	3.52	.001*	.040	.141
LICA volume flow rate	.002	.001	.225	2.82	.005*	.001	.003
RICA volume flow rate	-.003	.001	-.359	-4.51	.000*	-.005	-.002
LCCA volume flow rate	.002	.001	.283	3.45	.001*	.001	.004
RCCA volume flow rate	-.002	.001	-.239	-2.86	.005*	-.004	-.001

Note. R^2=.201; $p < .001$

Discussion

There is general consensus in the literature that the left and right cerebral hemispheres differ in anatomy and function (Cagnie et al., 2006). In normal subjects, handedness and footedness are significant predictors of cerebral dominance (Cagnie et al., 2006; Hugdahl & Westerhausen, 2010). While right-handers show strong left hemisphere dominance, left-handers are significantly more lateralised to the right hemisphere (Basic et al., 2004; Vivani et al., 1998). Right-left differences have been demonstrated in various aspects of cerebral vascularisation. A left sided dominance has been shown in vessel structures such as the circle of Willis (Orlandini, 1985), middle and anterior cerebral arteries (Leutin et al., 2004; Mazziotta & Phelps, 1984; Müller et al., 1991; Willis et al., 2002), vertebral arteries (Thiel, 1991; Huang et al., 1993; Macchi et al., 1996) and ICAs (Carmon & Gamos, 1970; Bogren et al., 1994; Ogle, 1871). It is therefore surprising that the hemodynamic asymmetries of the cerebral vascular system have never been holistically, accurately, and systematically investigated in relation to hemispheric lateralisation of function — with a particular emphasis on the large calibre carotid arteries that contribute most significantly to cerebral perfusion.

This chapter provides a systematic quantification of the hemodynamic properties of the CCAs, ICAs, and ECAs between handedness groups in normotensive subjects. Hemodynamic parameters and sex differences were consistent with normative measures (Blizhevsky, Azhari, Gaitinit, & Dinnar, 1997; Goubergrits, Affeld, Fernandez-Britto, & Falcon, 2002; Holdsworth et al., 1999; Kamenskiy, et al., 2011; Krejza et al., 2006; Müller et al., 1987; Scheel et al., 2000).

The results provide evidence confirming the main research hypothesis. The analysis revealed considerable asymmetries between the hemodynamic properties of the left and right CCAs and ICAs of healthy left-handed and right-handed participants — with significantly higher blood flow in the arteries contralateral to the dominant hand. While left-handers demonstrated increased blood flow on the right, right-handers showed increased blood flow on the left. This was evident in the variables of diameter, mean velocity and volume flow rate, and it is validated by the high effect sizes.

There were no significant differences in systolic and diastolic BPs between the left and right arms in left-handed and ambidextrous participants. However, right-handers showed a significant right arm bias for systolic pressures, and a significant left arm bias for diastolic pressures (Table 3.2). Since systolic pressure is a reflection of the force that blood exerts against the arterial walls during ventricular systole (McArdle, Katch, & Katch, 2010), right-handers have a significantly greater surge of blood to their dominant arm through the right brachial artery as opposed to the left. Diastolic pressure, on the other hand, indicates peripheral resistance (McArdle, Katch, & Katch, 2010). Therefore, pressure in the left brachial artery of right-handers does not dissipate as rapidly as the right after systole, indicating a significantly greater peripheral resistance in the left arm. This variability is not considered pathological. Asymmetry between bilateral systolic BP determinations of both arms has been reported in the literature (Pesola, Pesola, Nelson, & Westfal, 2001).

Diameters, mean blood flow velocities, and blood volume rates of the CCAs and ICAs showed a significant inverse handedness-related asymmetry (Figure 3.9). In right-handers, these hemodynamic characteristics were consistently higher in the arteries contralateral to hand dominance. Therefore, right-handers had significantly greater diameters, faster velocities and higher blood volumes in the LCCA and LICA.

Left-handers also showed a significant inverse handedness-related asymmetry at the level of the ICA— but this was in the opposite direction to right-handers. Therefore, left-handers had significantly greater diameters, faster velocities and higher blood volumes in the right ICA. This was less so at the level of the CCA. Although carotid diameters were significantly greater on the right side in left-handers, left-handers showed negligible differences in blood flow velocities, and total blood volume flow rates. It is noteworthy, however, that RCCA mean velocities and volume flow rates were significantly faster and higher in left-handers than in any other handedness group.

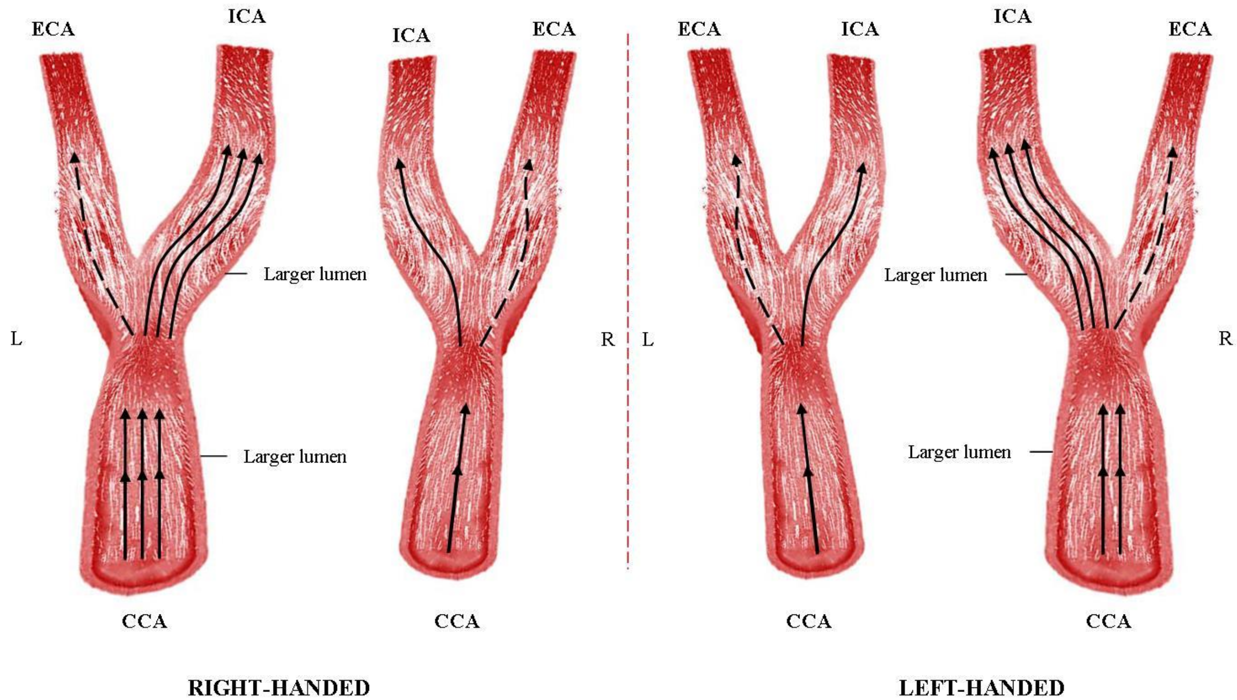

Figure 3.9. Schematic illustration of side-to-side asymmetries in the carotid arteries of right- and left-handers. Significantly higher blood volume flow rate and mean velocity represented with three arrows; larger flow volume rates represented with two arrows; equal hemodynamics represented with one arrow and flow negligible for handedness represented with dotted arrow. Diameter differences are also indicated in the figure.

Despite negligible differences in the diameters and blood flow velocities recorded in the CCAs, ambidextrous participants showed a blood volume asymmetry akin to right-handers (with higher volumes in the left). Nevertheless, no notable asymmetries are evident in either of these hemodynamic variables in the ICAs.

Although PI and RI are determined by a number of factors (Adamson, 1999) and should therefore be interpreted with caution (Czosnyka, Richards, Whitehouse, & Pickard, 1996), these parameters nevertheless have value (Frauchigner, Schmid, Roedel, Moosman, & Staub, 2001; Sharma, Tsivgoulis, Lao, Malkoff, & Alexandrov, 2007). Handedness did not play a role in resistance and pulsitility differences between the left and right arterial pathways. Therefore, despite higher and faster flows in the arteries contralateral to hand dominance, the resistance and pulsitility characteristics of the arteries remain stable. It is noteworthy that, at the level of the CCAs, these variables tend to be higher on the left side in right- and left-handers, but are only significantly larger in right-handers at the level of the ICA. This indicates a significantly greater hemodynamic stress of the LICA in right-handers. Since RI is significantly correlated with intima-media wall thickness, $r = 0.57$, $p < .001$ (Frauchigner et al., 2001), this is in keeping with studies of intima-media wall thickening, which report higher wall thickness and hemodynamic stress on the left side (Denarie et al., 2000; Lemme et al., 1995; Oxenham & Sharpe, 2003; Rodriguez-Hernandez et al., 2003; Simon et al., 2002).

These findings are consistent with the study hypothesis and validate the findings of the geometric analysis in Chapter 2. Furthermore, this study supports the early handedness-blood flow theory proposed by Ogle (1871) and de Fleury (1873). The results reflect asymmetries found in existing research regarding arterial diameter (Ogle, 1871; Müller et al., 1991), and flow rates (Bogren et al., 1994; Donis et al., 1988; Holdsworth et al., 1999; Luo et al., 2011; Schöning, Walter & Scheel, 1994; Zbornikova & Lassvik, 1986). Other studies have found negligible or converse asymmetries between the arteries. However, these studies used small sample sizes, failed to directly investigate minimum diameters, and failed to assess handedness in their subjects (Bennecke, 1878; Cunningham, 1902; Critchton-Browne, 1907; Scheel et al., 2000; Limbu et al., 2006; Manbachi et al., 2011).

While 83.5% of right-handers showed higher flow volume rates in the arterial structures feeding the left hemisphere, 69.4% of left-handers showed higher flow rates on the right, with 50% of ambidextrous individuals showing either asymmetry.

Volume flow rate in the CCAs and ICAs significantly differentiated between left- and right-handers. It is important to note, however, that it is the variability in flow volumes of the arteries feeding the right hemisphere that significantly differentiated between handedness groups. Although an impressive 93.7% of right-handers were correctly classified by the model, only 53.7% of left-handers were correctly classified. This is not surprising since the left-handed population is heterogeneous with respect to the direction of lateralisation, with approximately 60% being dominant in the left hemisphere (Roberts, 1969).

Blood flow volume rates also successfully predicted the degree of hand-proficiency, as determined by the participants' TI scores. However, this was most successful for hand speed. More specifically, flow volume rates in the ICAs were the best predictors of hand-proficiency — where higher flow rates in the arteries feeding the right hemisphere were associated with higher proficiency in the left hand, and higher flow volumes in arteries feeding the left hemisphere were associated with higher proficiency in the right hand.

Handedness did not influence the hemodynamic properties of the ECAs. However, left-handers had significantly faster velocities and greater flow volumes on both right and left ECAs compared to right-handed and ambidextrous participants.

Implications

The findings of this study may have implications for cerebrovascular pathology. Hemodynamic processes, such as changes in blood pressure parameters and the speed of the pressure wave propagation, play an important role in the development of vascular disease (Baldassarre et al., 2000; Glagov et al., 1988; O'Leary et al., 1999). It has long been known that excessive deformation and stress in the arterial wall compromise the integrity of the endothelium. The deposition of platelets, smooth muscle cell proliferation, and slow accumulation of lipoproteins in these regions may eventually lead to the development or progression of arterial disease (Clowes, Reidy, & Clowes, 1983; Moore, 1983).

The findings of this study suggest greater hemodynamic stress in the left extracranial carotid arteries of right-handed participants. This is in keeping with earlier publications that have reported larger hemodynamic stress, intimal damage, and intima-media wall thickness is the LCCA (Denarie et al., 2000; Önbaş et al., 2007; Rodriguez-Hernandez et al., 2003). More importantly, this increased hemodynamic stress reflects a handedness bias as it is larger in right-handers compared to left-handers (Önbaş et al., 2007). It is therefore, not surprising that a predilection for cerebrovascular disease in the left hemisphere exists (Rodriguez-Hernandez et al., 2003) and that left-handed and ambidextrous patients have a lower risk of sudden death of brain infarction (typically associated with left-sided stroke; Algra et al., 2003).

Further research will be needed to investigate the extent to which the handedness differences in the respective hemodynamic variables may influence cardiovascular morbidity and mortality, and whether these differences may directly predict the localisation of cerebrovascular pathology.

Summary and Conclusions

The physical mechanism of human cerebral lateralization has not yet been determined. The quantification of asymmetries between the extracranial arterial branches feeding the left and right cerebral hemispheres provides new insight into a potential anatomical mechanism of cerebral lateralisation. The geometric and hemodynamic findings suggest that the carotid arteries are anatomically and physiologically asymmetrical in a direction that promotes blood supply to the cerebral hemisphere dominant for handedness. This asymmetry shows high effect sizes, validating the practical significance of the findings.

This correlation between handedness and blood flow asymmetry suggests a putative anatomical mechanism for handedness and for cerebral lateralization in general. A blood flow supply increase of 19% is required to sustain a 5% increase in localized cerebral oxygen metabolic demand (Buxton and Frank, 1997). Our findings showed that, on average, participants with a left-biased supply have 53.52% lower arterial resistance and 19.01% higher blood flow rates in the LCCAs, and 25.61% higher flow rates in the LICA, which would support approximately 6.74% increased metabolic demand of the left hemisphere. Conversely, those with a right-biased supply have, on average, 28.95% lower arterial resistance and 17.52% higher flow rates in the RCCAs, and 17.59% higher flow rates in the RICA, which would support approximately 4.64% increased metabolic demand of the right hemisphere.

The characteristics of ambidextrous participants suggest the possible interplay of right-handed and left-handed asymmetries. The geometric properties of participants with unconventional arterial branching patterns produced a significantly greater overall resistance to blood flow in both vessels. However, a handedness-related bias was maintained through increased asymmetry of particular geometric properties.

No causal relationship can be concluded from this study. Although causality can be inferred from the lack of side-to-side arterial changes with age, it is not clear whether the arterial asymmetries identified cause handedness or are as a result of hemispheric dominance. Developmental studies should be conducted to further address this issue.

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APPENDIX A

Revised Edinburgh Handedness Inventory (English)

Indicate hand preference in the following activities:

Score	Always left 1	Usually left 2	No preference 3	Usually right 4	Always right 5
1. Writing					
2. Throwing a ball					
3. Cutting with scissors					
4. Brushing teeth					
5. Using a knife (without a fork)					
6. Eating with a spoon					
7. Striking a match (match)					
8. Opening a box (lid)					
9. Kicking a ball					
10. Using a computer mouse					

11. As a child, did you ever feel forced to use your right hand to complete tasks, when you were in fact more comfortable using the left? YES/NO

Appendix B

Revised Edinburgh Handedness Inventory (Afrikaans)

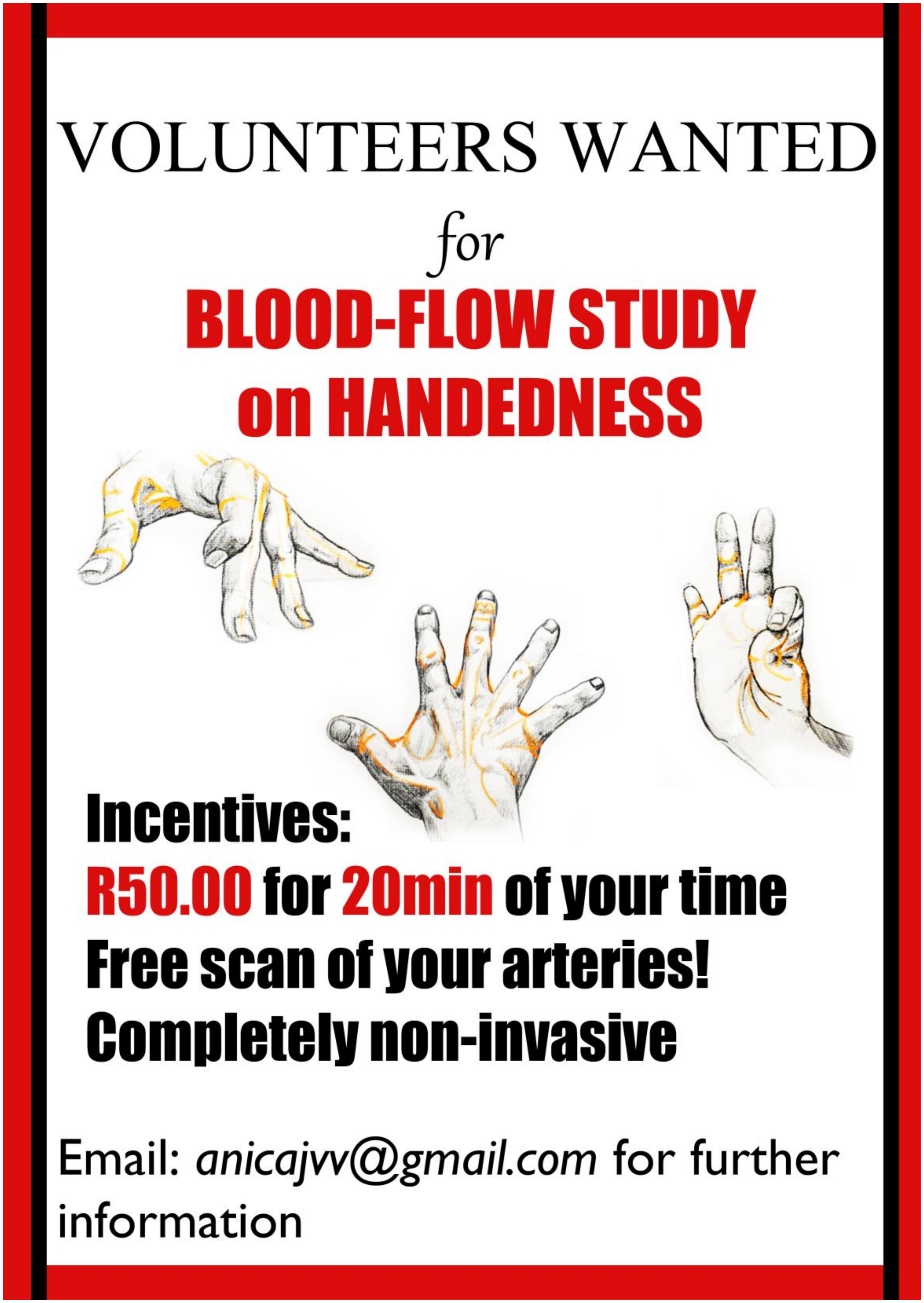
Dui jou handvoorkeuraan vir die volgende aktiwiteite:

Score	Altyd links 1	Gewoonlik links 2	Geen voorkeur 3	Gewoonlik regs 4	Altyd regs 5
1. Skryf					
2. ‘n Balgooi					
3. Met ‘n skêr sny					
4. Tande borsel					
5. Gebruik van ‘n mes (sonder ‘n vurk)					
6. Eet met ‘n lepel					
7. ‘n Vuurhoutjie trek					
8. ‘n Houer oopmaak (deksel)					
9. ‘n Balskop					
10. ‘n Rekenaar muis gebruik					

11. Was jy ooit as kind gedwing om jou regterhand te gebruik om take te verrig, terwyl jy in werklikheid gemakliker was om dit met jou linkerhand te doen? JA/NEE

APPENDIX C

Handedness Recruitment Poster



APPENDIX D

Description of Verbal Consent and Assent Process (English)

Verbal Consent

"Good morning, my name is Anica Jansen van Vuuren. I am a postgraduate student in the Department of Psychology at the University of Cape Town. I am affiliated with (name of hospital) and together we are doing a study on handedness in South Africa and its possible link to vascular asymmetry of the branches of the aortic arch. I would just like to speak to you briefly about the CTA scan you had at (name of hospital) on the (give date of scan). It will not take long, approximately 5 minutes. Are you able to speak to me?

We, at the department of Neuropsychology, are busy conducting research on handedness in South Africa and its possible link to vascular asymmetry of the branches of the aortic arch. In order for us to conduct the study, we need your permission to utilise the CTA scan, which is housed at the hospital, for the study. The information you share with me will be of great value in helping me to complete this research project, the results of which could significantly enhance our understanding of the origins of handedness.

This phonecall is to ask your permission for us to perform a geometric analysis on the CT scan so as to better understand the relationship between the structure of the arteries feeding the brain, and handedness (which means whether you are right-handed or left-handed). All this means is that we are interested in analysing the geometric structure of the arteries, such as the size of the arteries, their length, and their angles in the body. Therefore no medical or sensitive information will be involved in it at all.

This interview will take approximately seven minutes of your time. All information will be strictly confidential. Your data will be stored according to a coding number, so your identity will remain anonymous throughout this research project. Your CTA scans will only be handled by myself, Anica Jansen van Vuuren, and medical practitioners. If any previously undetected anatomical abnormalities are found during the CTA analysis, confidentiality may be broken in so far as the neurologist may then discuss the abnormality and possible medical treatment with you. There are no other expected risks of participation. Participation is voluntary. If you decide not to participate in the study or to withdraw your participation at any time you may do so with no consequences whatsoever. It is important to know, that your participation will not be compensated financially.

Feel free to ask me any questions about anything that I have said that may be unclear, or that you would like to know about (give time for questions). Do you agree to participate in this study?

… Thank you."

Verbal Assent

"Good morning, my name is Anica Jansen van Vuuren. I am a postgraduate student in the Department of Psychology at the University of Cape Town. I am affiliated with (name of hospital) and together we are doing a study on handedness in South Africa and its possible link to vascular asymmetry of the branches of the aortic arch. I would just like to speak to you briefly about the CTA scan your child (name of child) had at (name of hospital) on the (give date of scan). It will not take long, approximately 5 minutes. Are you able to speak to me?

We, at the department of Neuropsychology, are busy conducting research on handedness in South Africa and its possible link to vascular asymmetry of the branches of the aortic arch. In order for us to conduct the study, we need your permission to utilise your child's CTA scan, which is housed at the hospital, for the study. The information you share with me will be of great value in helping me to complete this research project, the results of which could significantly enhance our understanding of the origins of handedness.

This phonecall is to ask your permission for us to perform a geometric analysis on the CT scan so as to better understand the relationship between the structure of the arteries feeding the brain, and handedness (which means whether you are right-handed or left-handed). All this means is that we are interested in analysing the geometric structure of the arteries, such as the size of the arteries, their length, and their angles in the body. Therefore no medical or sensitive information will be involved in it at all.

This interview will take approximately seven minutes of your time. All information will be strictly confidential. Your child's data will be stored according to a coding number, so his/her identity will remain anonymous throughout this research project. Their CTA scans will only be handled by myself, Anica Jansen van Vuuren, and medical practitioners. If any previously undetected anatomical abnormalities are found during the CTA analysis, confidentiality may be broken in so far as the neurologist may then discuss the abnormality and possible medical treatment with you. There are no other expected risks of participation. Participation is voluntary. If you decide not to let your child participate in the study or to withdraw his/her participation at any time you may do so with no consequences whatsoever. It is important to know, that your participation will not be compensated financially.

Feel free to ask me any questions about anything that I have said that may be unclear, or that you would like to know about (give time for questions). Do you agree to participate in this study?

… Thank you."

APPENDIX E

Description of Verbal Consent and Assent Processes (Afrikaans)

Vebral Consent

“Goeie more, my naam is Anica Jansen van Vuuren. Ek is ‘n nagraadse student in die Departement Sielkunde by die Universiteit van Kaapstad. Ek is geassosieerd met (naam van die Hospitaal), en ek wil asseblief met u gesels oor die CT skandering wat u op die (datum van skandering) by (naam van Hospitaal) ondergaan het. Dit gaan nie baie van u tyd opneem nie, so plus minus 5 minute. Is dit vir u nou geleë om met my te kan praat?

Ons, by die department van Neuro-Sielkunde, is besig om navorsing te doen oor links- en regshandigheid. Wat ons probeer vasstel is of daar ‘n moontlike verband is tussen links- en regshandigheid en die asimmetriese vaskulêre boog van die Aorta. Om ons in staat te stel om hierdie navorsing te kan doen en te kan voltooi het ons u toestemming nodig om u CT skandering, wat ek reeds na verwys het, te ondersoek en te gebruik. Aldus, die rede van my oproep. U toestemming sal van groot waarde wees en sal hoog op prys gestel word.

Die inligting van u CT skandering wat ons baie graag wil gebruik, is die grootte en struktuur van u slagaar (Aorta), die lengte, en die eienskappe van die boog daarvan. Alle inligting sal streng vertroulik gehou word. Dit sal volgens ‘n kode gestoor word, en u identiteit sal deurgaans tydens die en na die navorsingsprojek anoniem bly. Wat beteken dat u CT skandering slegs deur my, Anica Jansen van Vuuren, en die betrokke Medici hanteer sal word.

Let wel dat indien indien enige voorheen nie gediagnoseerde anatomiese abnormaliteit tydens u CT analise opgespoor word, kan die vertroulikheid moontlik verbreek word in soverre die Neuroloog moontlik die abnormaliteite en moontlike behandeling daarvan met u sal wil bespreek. Daar is geen ander verwagte risiko’s verbonde aan u deelname nie. U deelname is heeltemal vrywillig en indien u sou besluit om nie aan die studie deel te neem nie of op enige tydstip u aan die studie wil onttrek, mag u dit doen sonder enige gevolge hoegenaamd. Let ook asseblief daarop dat daar ongelukkig ook nie ‘n finansiële gewin vir u vir die gebruik van u CT skandering is nie.

Wees asseblief vry om enige vrae te vra wat vir u onduidelik is, of om te vra vir meer inligting alvorens u besluit om aan die studie deel te neem. (… gee tyd vir vrae …)

Stem u daartoe in om aan hierdie studie deel te neem?

Dankie vir u tyd en toestemming. ”

Verbal Assent

“Goeie more, my naam is Anica Jansen van Vuuren. Ek is ‘n nagraadse student in die Departement Sielkunde by die Universiteit van Kaapstad. Ek is geassosieerd met (… naam van die Hospitaal …), en ek wil asseblief met u gesels oor die CT skandering wat u se kind (…naam van kind…) op die (… datum van skandering …) by (… naam van Hospitaal …) ondergaan het. Dit gaan nie baie van u tyd opneem nie, so plus minus 5 minute. Is dit vir u nou geleë om met my te kan praat?

Ons, by die department van Neuro-Sielkunde, is besig om navorsing te doen oor links- en regshandigheid. Wat ons probeer vasstel is of daar ‘n moontlike verband is tussen links- en regshandigheid en die asimmetriese vaskulêre boog van die Aorta. Om ons in staat te stel om hierdie navorsing te kan doen en te kan voltooi het ons u toestemming nodig om u se kind se CT skandering, wat ek reeds na verwys het, te ondersoek en te gebruik. Aldus, die rede van my oproep. U toestemming sal van groot waarde wees en sal hoog op prys gestel word.

Die inligting van u se kind se CT skandering wat ons baie graag wil gebruik, is die grootte en struktuur van u slagaar (Aorta), die lengte, en die eienskappe van die boog daarvan. Alle inligting sal streng vertroulik gehou word. Dit sal volgens ‘n kode gestoor word, en u identiteit sal deurgaans tydens die en na die navorsingsprojek anoniem bly. Wat beteken dat u se kind se CT skandering slegs deur my, Anica Jansen van Vuuren, en die betrokke Medici hanteer sal word.

Let wel dat indien indien enige voorheen nie gediagnoseerde anatomiese abnormaliteit tydens u se kind se CT analise opgespoor word, kan die vertroulikheid moontlik verbreek word in soverre die Neuroloog moontlik die abnormaliteite en moontlike behandeling daarvan met u sal wil bespreek. Daar is geen ander verwagte risiko's verbonde aan u deelname nie. U deelname is heeltemal vrywillig en indien u sou besluit om nie u se kind aan die studie deel te neem nie of op enige tydstip u u se kind aan die studie wil onttrek, mag u dit doen sonder enige gevolge hoegenaamd. Let ook asseblief daarop dat daar ongelukkig ook nie 'n finansiële gewin vir u vir die gebruik van u CT skandering is nie.

Wees asseblief vry om enige vrae te vra wat vir u onduidelik is, of om te vra vir meer inligting alvorens u besluit om aan die studie deel te neem. (… gee tyd vir vrae …)

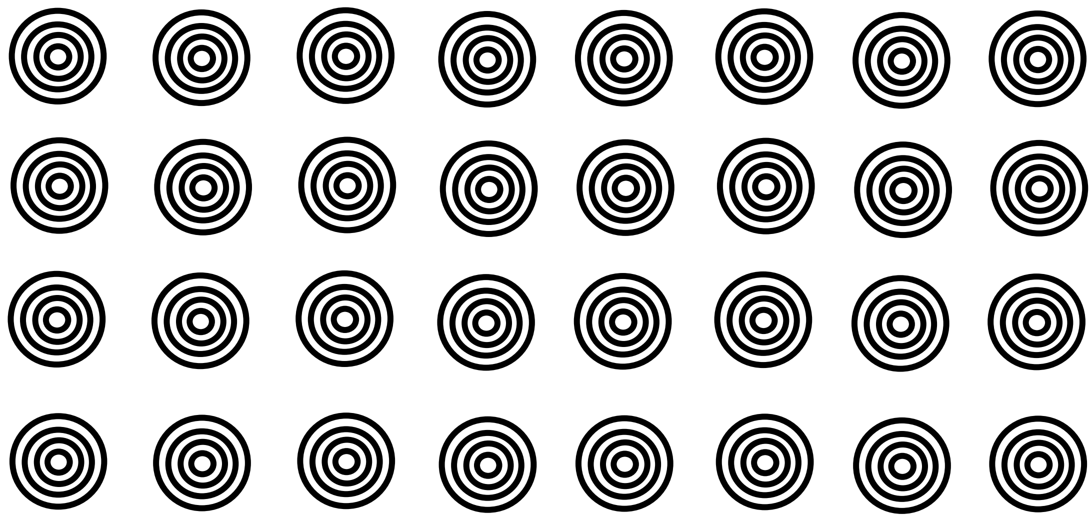
Stem u daartoe in om aan hierdie studie deel te neem?

Dankie vir u tyd en toestemming. "

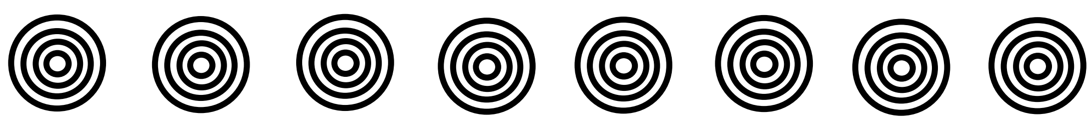
APPENDIX F

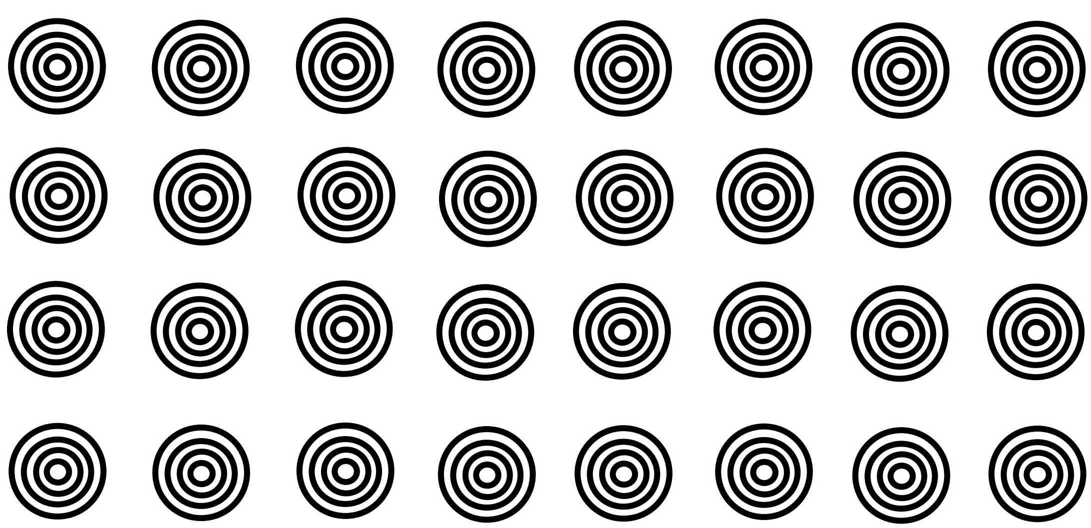
Target Test Form

RIGHT HAND



PRACTICE ROW





LEFT HAND

PARTICIPANT NUMBER ________

AGE ________

SEX ________

APPENDIX G

Consent Form for Hemodynamic Analysis

Informed Consent to Participate in Research and Authorization for Collection, Use, and Disclosure of Protected Health Information

This form provides you with information about the study and seeks your authorization for the collection, use and disclosure of your protected health information necessary for the study.

The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions.

Your participation is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. By participating in this study you will not be penalized or lose any benefits to which you would otherwise be entitled.

1. Name of Participant ("Study Subject")

____

2. Title of Research Study

Relationship between handedness and the geometry and hemodynamic characteristics of the branches of the aortic arch.

3. Principal Investigators, Ethics Committee, and Telephone Numbers

Prof Mark Solms

Department of Psychology

University of Cape Town

Mark.solms@uct.ac.za

Faculty of Health Sciences

Research Ethics Committee

Room E52-24 Groote Schuur Hospital Old Main Building

Observatory 7925

Tel: 021-406-6338; Fax: 021-406-6411

Email: lamees.emjedi@uct.ac.za

4. What is the purpose of this research study?

The purpose of this research study is to explore the relationship between the geometric and hemodynamic characteristics of the branches of the aortic arch and handedness and thereby lateralisation of cognitive functioning. More specifically, we are interested in the differences in blood flow of the common carotid arteries at rest.

5. What will be done if you take part in this research study?

This study requires you to take part in one research session. On that day you will need to complete a 10 item Edinburg handedness Inventory (approximately 3 min), complete a speed and accuracy Target Test (approximately 5 min), and a non-invasive Doppler ultrasound analysis of your left and right common carotid arteries (approximately 20 min). The ultrasound will be analysed for hemodynamic asymmetries.

6. What are the possible discomforts and risks?

There are no other discomforts and risks associated with participation in the study.

7. What are the possible benefits of this study?

One major benefit of this study is that scientists and society in general, will have better understanding of the role arterial blood flow plays in handedness and hemispheric lateralisation. This knowledge has both clinical and scientific importance.

8. Can you withdraw from this research study and if you withdraw, can information about you still be used and/or collected?

You may withdraw your consent and stop participation in this study at any time. Information already collected may be used.

9. Once personal information is collected, how will it be kept confidential in order to protect your privacy and what protected health information about you may be collected, used and shared with others?

Information collected will be stored in locked filing cabinets or in computers with security passwords. Only certain people - the researchers for this study - have the legal right to review these research records. Your research records will not be released without your permission unless required by law or a court order. If you agree to be in this research study, it is possible that some of the information collected might be copied into a "limited data set" to be used for other research purposes. If so, the limited data set may only include information that does not directly identify you.

10. Signatures

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternatives to being in the study;

and how the participant's protected health information will be collected, used, and shared with others:

____ ____________________

Signature of Person Obtaining Consent and Authorization Date

You have been informed about this study's purpose, procedures, and risks; how your protected health information will be collected, used and shared with others. You have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information. By signing this form, you are not waiving any of your legal rights.

____ ____________________

Signature of Person Consenting and Authorizing Date

Please indicate below if you would like to be notified of future research projects conducted by our research group:

______________ (initial) Yes, I would like to be added to your research participation pool and be notified of research projects in which I might participate in the future.

Method of contact:

Phone number: ________________________________

E-mail address: ________________________________

Mailing address: ________________________________

____

____