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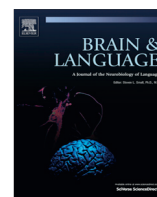
Structural asymmetry of anterior insula: Behavioral correlates and individual differences

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ABSTRACT

The current study investigated behavioral correlates of structural asymmetry of the insula, and traditional perisylvian language regions, in a large sample of young adults ($N = 200$). The findings indicated (1) reliable leftward surface area asymmetry of the anterior insula, (2) association of this asymmetry with divided visual field lateralization of visual word recognition, and (3) modulation of the correlation of structural and linguistic asymmetry by consistency of hand preference. Although leftward asymmetry of cortical surface area was observed for the anterior insula, pars opercularis and triangularis, and planum temporale, only the anterior insula asymmetry was associated with lateralized word recognition. We interpret these findings within the context of recent structural and functional findings about the human insula. We suggest that leftward structural lateralization of earlier developing insular cortex may bootstrap asymmetrical functional lateralization even if the insula is only a minor component of the adult language network.

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1. Introduction

Ideas about cortical regions recruited for language processing have evolved considerably in recent decades. In addition to classical language areas in left perisylvian cortex, a much more widespread network spanning both hemispheres has been shown to participate in language functions (Hickok & Poeppel, 2007; Price, 2010). Hence, one goal of contemporary research is to identify the functional significance of various components of this network, and to examine individual differences in brain organization for language. In most individuals during language tasks, regions within the left hemisphere respond with greater activation (Price, 2010) and synchronization (Saur et al., 2010) than comparable right hemisphere regions. Left hemisphere language specialization is also observable using behavioral techniques that lateralize initial receipt of verbal information to a single hemisphere (Bryden, 1982; Chiarello, 1988).

Numerous structural asymmetries have been identified in language relevant cortex (Foundas, Eure, Luevano, & Weinberger, 1998; Watkins et al., 2001), although the association between structural and functional lateralization is tenuous (Eckert, Leonard, Possing, & Binder, 2006). The left inferior frontal gyrus (pars triangularis and opercularis) and superior temporal plane (planum temporale and surrounding temporal–parietal areas) represent quintessential language cortex, and are structurally and/or functionally asymmetric (Chiarello, Welcome, Halderman, & Leonard, 2009; Price, 2012). Wernicke initially suggested that the insula might also be important for language function (Wernicke (1874) as cited by Weiller, Bormann, Saur, Musso, and Rijntjes (2011)), and in 1908, Augusta Dejerine-Klumpke described anatomical evidence that lesions to an area deep to the left pars opercularis including the anterior insula was associated with nonfluent aphasia (Roch Lecours & Caplan, 1984). Recent research implicates the insula in a wide variety of cognitive, sensory, and emotional functions (Menon & Uddin, 2010; Mutschler et al., 2009). Nieuwenhuys (2012), for example, lists over 15 different putative insula specializations. Functional neuroimaging and lesion studies also suggest participation of the insula in some language tasks (Dronkers, 1996; Mutschler et al., 2009), and one recent study claimed that insular volume asymmetry could predict functional language lateralization (Keller et al., 2011). However, the interpretation of some findings has been challenged (Hillis et al., 2004; Richardson, Fillmore, Rorden, LaPointe, & Fridriksson, 2012), and the very diversity of suggested insula functions raises questions about whether this region may subserve any language-specific processes.

The extent to which the human insula is asymmetrical in either structure or function is not well understood and requires further examination. In the current investigation, we examine structural asymmetry of the insula, and potential behavioral correlates, along with asymmetry in more traditional language regions. This

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research had several objectives. First, to document the extent of structural asymmetry, we measured asymmetries of cortical surface area in classical frontal and temporal language regions and in the insula in a large sample of healthy young adults. Second, we assessed the degree of association between these structural asymmetries and lateralized language processing using a composite measure of visual word recognition. If the insula participates in the language network, then we would expect a structure/function association that is at least as strong for the insula as for more traditional language areas. We additionally investigated the association between structural asymmetry and reading skill. Third, we considered whether consistency of hand preference affects structural asymmetries and structure/behavior relationships. Although behavioral differences have been documented between individuals with consistent and mixed hand preferences (see Prichard, Propper, & Christman, 2013 for recent review), the neural correlates of these differences have been largely unexplored. To preview our findings, we document herein (1) reliable leftward surface area asymmetry of the anterior insula, (2) the association of this asymmetry with lateralization of visual word recognition, and (3) modulation of the correlation of structural and linguistic asymmetry by consistency of hand preference. Before presenting these results, we present a brief review of relevant structural and behavioral investigations.

1.1. Regional structural and functional organization of human insula

The human insula has an approximately trapezoidal shape and in most individuals consists of 5 gyri, 3 anterior (short insular) and 2 posterior (long insular) gyri, separated by the deep central sulcus of the insula (Afif & Mertens, 2010). Although early cytoarchitectural research reported that the central sulcus of the insula approximated the boundary between agranular (anterior) and granular (posterior) cortex, a recent review and reanalysis supported a more concentric ventral to dorsocaudal organization (Nieuwenhuys, 2012). Comparative studies suggest an expansion of the anterior insula that may be associated with increased complexity of cognitive functions across mammalian species (Nieuwenhuys, 2012). The white matter organization of the insular region includes the extreme capsule, a portion of a ventral language pathway, that courses beneath the insular cortex (Axer, Klingner, & Prescher, in press).

Probabilistic tractography studies have documented gradual shifts in connectivity patterns between anterior and posterior insular regions (Cerliani et al., 2012; Cloutman, Binney, Drakesmith, Parker, & Ralph, 2012; Nanetti, Cerliani, Gazzola, Renken, & Keysers, 2009). The most anterior insular areas project to orbitofrontal cortex, pars triangularis and opercularis, and anterior temporal cortex, while the most posterior regions have projections to posterior STG and MTG and to somatosensory and posterior parietal cortex (Cerliani et al., 2012; Cloutman et al., 2012; Jakab, Molnar, Bogner, Beres, & Berenyi, 2011). A transitional pattern of connectivity was observed for intermediate insular regions (middle and posterior short gyri, anterior long gyrus) with projections to inferior frontal gyrus, premotor cortex, rolandic operculum, and temporal and parietal cortex (Cerliani et al., 2012; Cloutman et al., 2012). With respect to classical language areas, major projections were found between the dorsal anterior insula and BA 45, and from dorsal middle insula (middle and posterior short gyri) to BA 44 and 6. Hence the anterior insula had the highest connection probability with key frontal language areas (Cerliani et al., 2012). Resting state functional connectivity research also documents anterior to posterior insular shifts in connectivity, with additional dorsal/ventral differentiation of anterior insula functional connections (Cauda et al., 2011; Chang, Yarkoni, Khaw, & Sanfrey, in press; Deen, Pitskel, & Pelphrey, 2011). In particular, activity in dorsal anterior in-

sula was associated with activity in the anterior cingulate, orbitofrontal cortex, and dorsolateral frontal, temporal and parietal opercular cortex, while ventral anterior insula activity was associated with superior temporal sulcus, amygdala, and frontal and temporal opercula activation (Chang et al., in press; Deen et al., 2011).

Activation of the insula has been observed in a wide variety of functional neuroimaging tasks (Chang et al., in press; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010), and a number of broadly defined functions have been attributed to this brain region. As with structural findings, distinctions emerge between anterior and posterior insular regions. Posterior portions of the insula respond to visceral and interoceptive sensations, regulate physiological reactivity and homeostasis, and are involved in some sensorimotor functions, while anterior regions are more involved in introspecting about feelings (Craig, 2009; Kurth et al., 2010; Menon & Uddin, 2010). In addition, the anterior insula is hypothesized to play an important role in experiencing and interpreting social emotions (Lamm & Singer, 2010) and in social interaction (Guionnet et al., 2012). The perception of pain has also been linked to the insula (Nieuwenhuys, 2012), with recent fMRI evidence suggesting that the mid-posterior insula mediates the experience of pain, while the anterior insula is involved in the anticipatory anxiety of pain (Lin, Hsieh, Yeh, Lee, & Niddam, 2013). The anterior insula, along with the anterior cingulate, may function to detect and respond to salient stimuli (Menon & Uddin, 2010), and participate in attention and cognitive control processes (Menon & Uddin, 2010; Nelson et al., 2010). One model of insular function posits a posterior to anterior progression of processing from the representation of interoceptive sensations (posterior), to the integration of these sensations with emotionally salient environmental stimuli (middle), to awareness of the self in the immediate moment (anterior) (Craig, 2009). A recent meta-analysis of active task functional connectivity likewise identified an anterior cluster with long-range connections to regions involved in attention, and a posterior cluster with more local connectivity to sensorimotor regions (Cauda et al., 2012).

Meta-analyses across a wide variety of tasks indicate that the left and right anterior insula are some of the most frequently activated areas, implying a role in processes that are shared across many behaviors (Nelson et al., 2010), perhaps involving multimodal functional integration (Cauda et al., 2012; Kurth et al., 2010). It is becoming increasingly clear that a network perspective is important for understanding the role of the insula in perceptual and cognitive functions. Menon and Uddin (2010) identify the anterior insula and anterior cingulate as key components in a salience network which functions to select the most relevant internal and external stimuli for behavioral guidance. Furthermore, they posit that the anterior insula is critical for coordinating and switching between central executive and default mode networks, that is, to engage attention, working memory, and control processes while disengaging systems that are not currently relevant. Cauda et al. (2012) also identify the anterior insula as a hub that bridges anterior and posterior insular circuits. Such data raise the possibility that any insular involvement in language may involve the coordination or overlap of functional networks recruited for a broad variety of activities.

1.2. Evidence for insula asymmetry

Few studies have examined structural asymmetries in the insula. Two large scale studies using similar voxel based morphometry (VBM) methods reported slightly different results. Watkins et al. (2001) observed leftward asymmetry for gray matter in a superior portion of the anterior insula and the medial middle insula, and rightward asymmetry for a very inferior portion of the anterior in-

sula. Good et al. (2001), by contrast, reported leftward asymmetry of the posterior insula area adjacent to the anterior bank of Heschl's gyrus. A recent analysis of surface area asymmetries also reported leftward asymmetry of this posterior insula area (Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012), while a cytoarchitechtonic study of 10 brains found no suggestion of an asymmetry (Kurth et al., 2009).

Evidence for lateralization in structural or functional connectivity has also been inconsistent (Cauda et al., 2011; Cerliani et al., 2012; Cloutman et al., 2012; Deen et al., 2011; Jakab et al., 2011; Uddin, et al., 2010). In general, connectivity is similar across hemispheres (Cloutman et al., 2012; Deen et al., 2011; but see also Cauda et al., 2012). However, there is some evidence from both structural (Cerliani et al., 2012) and functional connectivity studies (Cauda et al., 2011) that the right insula communicates with a more diverse array of structures than the left (but see also Jakab et al., 2011).

There is some evidence for functional asymmetry of the anterior insula. It is notable that the right anterior insula plays a prominent role in awareness and saliency models (Craig, 2009; Menon & Uddin, 2010), and meta-analytic functional connectivity research identifies the right anterior insula as "a pivotal region in the attention systems of the brain" (Cauda et al., 2012, p. 352). The left anterior insula has been implicated in articulation, both overt and covert, and phonological working memory/inner speech (Kurth et al., 2010; Price, 2010, 2012). Patients with left anterior insula lesions may have deficits in speech planning and/or execution (Baldo, Wilkins, Ogar, Willock, & Dronkers, 2011; Dronkers, 1996; Ogar et al., 2006). However, the clinical evidence for insular involvement in speech production deficits has been contested (Hillis et al., 2004; Richardson et al., 2012). Progressive nonfluent aphasia may also be associated with hypometabolism and degeneration in the left anterior insula (Nestor et al., 2003; Seeley, 2010), although this area is not involved in cases of primary progressive apraxia of speech (Josephs et al., 2006, 2012). Functional neuroimaging studies document left insular activation in speech production tasks, particularly when production of foreign or unfamiliar speech sounds is required (Ackermann & Riecker, 2010; Bohland & Guenther, 2006; Eickhoff, Heim, Zilles, & Amunts, 2009; Moser et al., 2009; Shuster, 2009). Load dependent changes in left anterior insula activation have also been observed in phonological working memory tasks (Chee, Soon, Lee, & Pallier, 2004; Marvel & Desmond, 2012). Other language functions may also recruit the left anterior insula, such as rhyme detection (Hurschler, Liem, Jancke, & Meyer, 2012), sublexical phonological coding during reading (Borowsky et al., 2006; Price, 2012), and reading comprehension of actions (Saygin, Wilson, Dronkers, & Bates, 2004). Although the precise role of the left anterior insula is currently unsettled, there is accumulating evidence that this region may be recruited during some language tasks.

A recent investigation reported a link between structural insula asymmetry and functional language lateralization (Keller et al., 2011). In that study, 10 individuals with right hemisphere language dominance, and 15 with left hemisphere language dominance were selected from a large sample of over 600 healthy university students/graduates based on the direction of their functional language lateralization. All selected participants were right handed (mean age = 28 years), but degree or consistency of handedness was not investigated. Language dominance was determined by letter fluency tasks during either functional transcranial Doppler sonography (TCD) or fMRI (Keller et al., 2011), using measures for which there is considerable validity (c.f., Knecht et al., 1998; Knecht, Deppe, et al., 2000, Knecht, Drager, et al., 2000). Letters were presented visually for TCD and auditorily for fMRI. Volumetric structural asymmetries were estimated using stereology for the pars opercularis, pars triangularis, planum temporale and insula (see Keller et al., 2011 for details of measurement technique and

anatomical boundaries). Leftward structural asymmetries in pars opercularis, pars triangularis, and planum temporale were observed for both left and right language dominant individuals, but there was no relationship to functional language lateralization. By contrast, structural asymmetry of the insula was significantly correlated with language lateralization ($r = .47$). Remarkably, 80% of the left language dominant participants showed leftward structural asymmetry while nearly all (90%) of right dominant individuals showed rightward structural asymmetry. In this study, anterior and posterior insula asymmetries were not measured separately, although the authors comment that the structure/function asymmetry relation "was not localized to one particular region of the insula and is apparent in the anterior, middle, and posterior regions" (Keller et al., 2011, p. 2022 – see also their Fig. 6).

These findings are striking given that structure/function relations were observed for the insula, but not for more traditional language regions. However, the generalizability of the Keller et al. (2011) findings is not clear. First, their sample was small and intentionally not representative of the distribution of lateralization within the population. Hence it is unclear whether a similar structure/function association would be obtained in a less restricted sample, and whether there is population-wide asymmetry of insular cortex. Second, the extent of hemispheric specialization can vary by task, so it is important to seek corroboration with additional language measures. Third, it is unclear whether the findings for cortical volume were due to asymmetries in surface area and/or thickness. Fourth, the apparent absence of anterior/posterior insula differences stands in contrast to both anatomical and functional findings that document an anterior to posterior gradient within the insula as reviewed above. The coronal sections that Keller et al. (2011) examined do not respect sulcal boundaries within the insula (see their Figs. 3 and 6), so perhaps a sulcus-based parcellation could reveal anterior/posterior differences. Finally, as in most anatomical studies, potential effects of the degree or consistency of participant handedness were not examined. As reviewed briefly below, consistency of hand preference may represent an important dimension of individual difference, although the neuro-structural correlates of this variation remain to be determined.

1.3. Measurement of hand preference and recent behavioral findings

Investigations of brain organization and cerebral lateralization typically include only right-handed participants, or compare left- and right-handers. At the population level, left-handers are somewhat less likely than right-handers to demonstrate strong left hemisphere language lateralization (Bryden, 1982). However, scores on hand preference questionnaires fall on a continuum from strong, consistent right-handers to strong, consistent left-handers, and many investigators distinguish between those with strong, consistent hand preferences and those with more mixed preferences (e.g., Foundas, Leonard, & Hanna-Pladdy, 2002; Knecht, Drager, et al., 2000; Witelson, 1989). Degree of hand preference has been shown to affect the extent of structural and functional lateralization for language and other cognitive functions (Bourne, 2008; Foundas et al., 2002; Isaacs, Barr, Nelson, & Devinsky, 2006; Khedr, Hamed, Said, & Basahi, 2002; Knecht, Drager, et al., 2000). Nevertheless, investigators differ in the number of hand preference subgroups they investigate and the criteria for determining cut-offs between subgroups. Such studies, however, have in common the attempt to use individual differences in hand preference to predict individual differences in structural and functional lateralization.

However, a considerable number of studies have appeared recently that instead investigate the relationship between degree of handedness and individual differences in cognitive performance, with little attention given to neuroanatomical substrates. These studies have documented a variety of behavioral differences be-

tween consistent handers (individuals who profess a strong preference for one hand across all probed activities) and mixed handers (individuals who profess weaker and/or less consistent hand preferences) (Prichard et al., 2013). For example, mixed handers outperform consistent handers in episodic memory tasks (Christman & Butler, 2011; Propper, Christman, & Phaneuf, 2005), are more inclined to base recognition responses on "know" than on "remember" judgments (Propper & Christman, 2004), have lower false memory rates (Christman, Propper, & Dion, 2004), and earlier offsets of childhood amnesia (Christman, Propper, & Brown, 2006). Mixed handers also are better at foreign language vocabulary learning (Kempe, Brooks, & Christman, 2009), have greater flexibility in switching between categories in semantic fluency tasks (Sontam, Christman, & Jasper, 2009), and more equivalent access to dominant and subordinate word meanings than do consistent handers (Sontam & Christman, 2012). Mixed handers also appear more susceptible to persuasion (Christman, Henning, Geers, Propper, & Niebauer, 2008) and to sensory illusions (Niebauer, Aselage, & Schutte, 2002), and more readily update their perceptual representations (Christman, Sontam, & Jasper, 2009). Theoretical interpretation of these myriad behavioral differences has appealed to the notion that mixed/weak handers have a greater degree of interhemispheric interaction than do consistent handers (c.f., Christman et al., 2004, 2008; Niebauer et al., 2002; Propper et al., 2005). Hence it is claimed that the behavioral differences should be attributed to a difference in functional brain organization. Although this suggestion is plausible, there is currently no evidence for a variation in brain substrates between mixed and consistent handers, in general, or during the performance of the tasks described above.

In prior studies we have observed that mixed and consistent handers do <u>not</u> differ in corpus callosum area (Welcome et al., 2009), in manual asymmetry measurements of the length of planum temporale, Heschl's gyrus, or pars opercularis (Chiarello et al., 2007), in visual field (VF) asymmetry for lexical tasks (Chiarello, Welcome, Halderman, & Leonard, 2009), or in standardized reading measures (Chiarello, Welcome, Halderman, & Leonard, 2009). This implies that individual variation in anatomy, in reading, or in VF lateralization cannot be accounted for by consistency of handedness. However, we have observed differences between mixed and consistent handers in the relationship between some behavioral and anatomical domains. For example, VF lexical asymmetry predicts reading skill in consistent, but not mixed, handers (Chiarello, Welcome, Halderman, & Leonard, 2009). Corpus callosum area is negatively associated with VF asymmetry in consistent handed males, but positively associated in mixed handed females (Welcome et al., 2009). We have also observed that brain volume is positively correlated with VF asymmetry in consistent handers, while brain volume is positively correlated with nonlateralized reading measures in mixed handers (Chiarello, Welcome, Towler, Otto, & Leonard, 2008). Such results suggest that it is the <u>association between</u> anatomy and behavior that may differ across these handedness groups. This possibility will be explored further in the current investigation. Hence, the current study was designed to partially bridge between studies that investigate neurological correlates of hand preference, and those that document substantial cognitive differences between individuals with mixed or consistent hand preference.

1.4. Predictions

Automated measures of asymmetry in cortical surface area, volume, and thickness were acquired for a large sample of college students in the insula (anterior and posterior), pars opercularis and triangularis, and planum temporale. We assessed the association of these asymmetries with VF measures of word reading, and standardized reading tests, across the entire sample, and separately for consistent and mixed handers. We examined several predictions.

First, following Keller et al. (2011), we predicted leftward asymmetry of the insula and the other perisylvian regions. However, functional associations between the insula and cognitive and linguistic tasks are generally observed for the anterior insula only. Therefore, we predicted leftward asymmetry for the anterior, but not posterior, insula. Second, assuming Keller et al.'s (2011) findings can be confirmed in a larger, more representative sample, we predicted a positive association between insula asymmetry and VF asymmetry. Third, we expected this association to differ for mixed and consistent handers. Based on our prior findings, we predicted a stronger correlation between insula and VF asymmetry for consistent, than for mixed, handers.

2. Method

2.1. Participants

Two hundred university student volunteers (100 male) participated, receiving $100 compensation (mean age = 21.6 years; range 18–34). They were recruited as part of the Biological Substrates for Language project (Chiarello, Welcome, Halderman, & Leonard, 2009, Chiarello, Welcome, Halderman, Towler, et al., 2009; Leonard et al., 2008; Welcome et al., 2009). Subjects with a history of brain injury or disease or conditions incompatible with an MRI scan were excluded. A neuroradiologist reviewed all scans for pathology, and four additional participants were excluded from the final sample due to abnormal findings on the MRI. All were native English speakers with normal or corrected-to-normal vision. To assess handedness, a five-item preference questionnaire was utilized (Bryden, 1982). This questionnaire includes the five most reliable and valid items from the Edinburgh inventory[1] and yields an index ranging from +1.00 (extreme right handedness) to −1.00 (extreme left-handedness) (Bryden, 1977, 1982). Mean handedness score for our sample was +.71 (median = +.90). The distribution of handedness scores for the current sample is provided in Supplementary Fig. 1. We considered consistent handers to be those who scored either −1.0 or +1.0 on the hand preference questionnaire.[2] These individuals (N = 103, 59 female) reported no use of the nondominant hand for any activity; five were consistent left handers. The remaining 97 (41 female) participants were considered to be mixed handers (handedness scores from −.90 to +.90, mean = +0.49). Among the mixed handers, 78% wrote with the right hand. It should be noted that mixed handers are usually not ambidextrous and most have some degree of right hand preference. We also administered Annett's (2002) pegboard moving task as a measure of hand performance/skill. On this measure, consistent handers had a greater skill difference between dominant and nondominant hands than did mixed handers (differences of .86 and .61 s, respectively, t(198) = 2.63, p < .01). The consistent and mixed handers did not differ in age (21.7 years versus 21.5 years, respectively).

2.2. Divided visual field stimuli, procedure, and asymmetry calculation

We utilized a composite measure of divided visual field lexical processing to assess lateralized language processing (described in

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[1] The five items are: writing a message; drawing a picture; using a toothbrush; throwing a ball; and using a pair of scissors. Participants rate each item using a 5-point scale to indicate degree of preference for each activity.

[2] Prior behavioral research comparing mixed and consistent handers used a median split based on the longer Edinburgh questionnaire to form groups (see Prichard et al., 2013). Questionnaires with more items increase the likelihood that participants will endorse some use of the nondominant hand. The median handedness score of our sample using the briefer Bryden (1982) questionnaire was +.90, but many participants had this score (see Supplementary Fig. 1). Categorizing consistent handers as those with the most extreme scores (+1 or −1) achieved nearly equally sized groups, and hence dichotomized the sample in a similar way to that employed by the Christman group.

detail below). The divided visual field (DVF) methodology has been widely used for several decades to assess hemispheric specialization (Bryden, 1982). Stimuli briefly presented to the left or right of fixation are initially received by the contralateral hemisphere, and a large literature has documented quantitative and qualitative differences in language processing that vary with the hemisphere of input (e.g., Chiarello, 1988, 1991; Federmeier, Wlotko, & Meyer, 2008). ERP studies using DVF stimuli find that even late ERP components (N400, Late Positive Component – LPC) differ by the input hemisphere, suggesting that hemisphere-specific language processes can be assessed via lateralized visual input (Coulson & Severens, 2007; Federmeier et al., 2008). In addition, a recent MEG word naming study found that although responses to DVF words in the extrastriate cortex were faster and stronger for contralateral than ipsilateral stimuli, responses in the left fusiform gyrus and speech motor cortex were faster and stronger for RVF than LVF words (Barca et al., 2011). This implies that superior processing of RVF words can be linked to left hemisphere language specialization. Although the exact set of DVF tasks we employed here has not been used in fMRI research, language lateralization estimated using DVF stimuli corresponds well to that observed for the same participants using fMRI methods (Hunter & Brysbaert, 2008; Van der Hagen, Cai, Seurinck, & Brysbaert, 2011). Hence for studies utilizing large samples, DVF methods can provide an efficient and cost-effective means to assess language lateralization.

In a preliminary session, three subtests of the Woodcock Reading Mastery Test – Revised (WRMT-R, Woodcock, 1998) were administered. Word Attack requires pronunciation of increasingly difficult pseudowords, Word Identification requires reading aloud words of increasing difficulty, and Passage Comprehension involves reading texts and producing a sentence completion appropriate for each text.

Four subsequent test sessions were held on separate days in which participants completed seven lateralized word recognition tasks. All participants received tasks in the following order:

Lexical decision: 90 word and 90 nonword trials, keypress discrimination response, 125 ms exposure.
Word naming: 90 trials, pronounce word, 125 ms exposure.
Category generation: 82 trials, produce exemplar of stimulus noun category (e.g., FRUIT), 155 ms exposure.
Nonword naming: 90 trials, pronounce nonword, 150 ms exposure.
Masked word recognition: 100 trials, recognize word preceded and followed by 60 ms pattern mask (@#@#), two-alternative forced choice key press response, 30 ms exposure. The response alternatives differed by only a single letter.
Verb generation: 100 trials, produce verb associated with stimulus noun, 150 ms exposure.
Semantic decision: 120 trials, determine whether stimulus noun represents a naturally occurring or manmade object, key press response, 120 ms exposure.

On average, each session was separated by 4 days. Each task was preceded by 30–48 practice trials.

Experimental stimuli consisted of 3–6 letter concrete nouns and/or pronounceable nonwords. Nonwords were created by replacing a single letter of a concrete noun, with each position of replacement occurring equally often. No stimuli were repeated within an experimental session, and no stimulus was shown more than twice throughout the study. Word lists for each task were equated for word length and log-transformed word frequency based on the Hyperspace Analogue to Language corpus (Lund & Burgess, 1996). Within each task, items were matched across visual field conditions on the basis of length (range 4.44–4.64 across

tasks), log frequency (range 4.17–4.71) (Lund & Burgess, 1996), familiarity and imageability (Wilson, 1988).

All stimuli were presented in uppercase, black 20 point Helvetica font on a white background on an Apple Studio Display M7649 monitor. Macintosh computers were used for stimulus presentation and recording of manual responses in the visual field tasks. Psyscope programming software (Cohen, MacWhinney, Flatt, & Provost, 1993) was used to control experimental events and record responses. Participants were seated 60 cm in front of the monitor, using a headrest to stabilize head position. For tasks requiring manual responses (Lexical Decision, Masked Word Recognition, and Semantic Decision), participants used the index fingers of each hand on the '.' and 'x' keys to indicate one response and the middle fingers of each hand on the '/' and 'z' keys to indicate the other response. This configuration was designed to accommodate both left- and right-handed participants. A Sony ECM-MS907 microphone was used to register vocal responses. Vocal responses were entered into the data file by an experimenter. Trials with spurious vocal responses (a cough, for example) or failures to respond were not analyzed.

Stimuli were randomly presented to the left or right visual field (LVF, RVF), 1.8° eccentric from a central fixation "+". At the onset of each trial, the fixation marker appeared for 600–805 ms and flickered just prior to the onset of the stimulus. Participants were instructed to maintain fixation and respond as quickly and accurately as possible.

Inverse efficiency (IE) scores were used as the primary dependent measure for each task as this measure takes into account both RT and accuracy (Townsend & Ashby, 1983; see Cherry et al., 2010 for application to divided visual field data). IE is computed by dividing mean reaction time by mean percent correct. A standard asymmetry index was then computed $[(LVF_{IE} - RVF_{IE})/(LVF_{IE} + RVF_{IE})]$. Composite measures are more reliable than any single assessment (Rosenthal, 2005), and we have found a composite lexical asymmetry score across tasks to be the most stable measure of word reading asymmetry (see Chiarello, Kacinik, Manowitz, Otto, & Leonard, 2004; Chiarello, Welcome, Halderman, & Leonard, 2009, Chiarello, Welcome, Halderman, Towler, et al., 2009). To create the composite asymmetry measure, scores for each task were z-scored, and then the z-scored asymmetries were averaged across tasks.

2.3. Image processing and anatomical measurements

Two MRI scans were obtained for each participant on a 1.5-T GE Signa scanner (3-D SPGR, 1.2 mm thick sagittal images). Imaging parameters: TR 11 ms, TE 2.2 ms, flip angle 25°, field of view 24 cm, acquisition time 4.36 min. Cortical reconstruction and volumetric segmentation was performed using the FreeSurfer v 4.5 analysis suite (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999) which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Briefly, processing includes motion correction and coregistration of T1 weighted images, removal of non-brain tissue, automated Talairach transformation, segmentation of deep gray and subcortical white matter volumetric structures, intensity normalization, tessellation of gray and white matter boundaries, automated topology correction, and surface deformation after intensity gradients optimally identify boundaries based on greatest intensity shifts. Manual inspection of the gray/white segmentation for all 400 hemispheres was performed.

Once the cortical models were complete, parcellation of the cerebral cortex into units based on gyral and sulcal structure, and a variety of surface based data including maps of cortical thickness representations were created using both intensity and continuity information from the entire three dimensional MR volume. Procedures for the measurement of cortical thickness have been

validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Free-surfer morphometric procedures have been demonstrated to show good test–retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter, Schmansky, Rosas, & Fischl, 2012).

Cortical surface area (pial area), volume, and thickness values were automatically extracted for left and right hemispheres by the FreeSurfer software. During processing, surface images were produced and mapped onto an averaged surface for each hemisphere where the parcellations were performed. The individual surfaces were then nonlinearly warped back into individual subject space. We examined the following parcellations produced by FreeSurfer's automated procedure: short insular gyri (henceforth, anterior insula), long insular gyrus and central sulcus of insula (henceforth posterior insula), pars triangularis, pars opercularis, and planum temporale. All of these areas have been reported to have acceptable automated/manual concordances, with mean concordance values of .77 (anterior insula), .79 (posterior insula), .79 (pars triangularis), .81 (pars opercularis), and .84 planum temporale (Destrieux, Fischl, Dale, & Halgren, 2010). Asymmetries for each parcellation were calculated by subtracting the right measure from the left and dividing by the average, so that leftward asymmetries yielded positive coefficients. Intracranial volume values from FreeSurfer were also extracted to be used as covariates in some analyses.

2.4. Statistical analyses

Univariate analyses were conducted for each of the five cortical regions to evaluate statistical significance of the regional asymmetries. Pearson correlations evaluated the association between anatomical and behavioral asymmetries, as well as between anatomical asymmetry and the reading subtest scores for each brain region. These analyses were conducted over the entire sample, and separately for the consistent and mixed handed groups. Simultaneous multiple regression analyses examined whether the critical anatomical/behavioral correlations were moderated by potentially confounding variables such as sex and intracranial volume.

3. Results

All analyses described here were conducted for surface area, volume, and thickness measures. In general, findings for volume paralleled those obtained for surface area. Surface area results are reported below, as this measure provided the most robust correlations. Comparable analyses for cortical volume and thickness are given in Supplementary materials. Examples of the FreeSurfer surface area parcellations for two participants are shown in Fig. 1.

3.1. Anatomical asymmetry findings

Mean surface area asymmetries for the anterior and posterior insula, and pars triangularis, opercularis and planum temporale are provided in Table 1 for the entire sample and each hand consistency group (see Suppl. Table 1 for volume and thickness means). Positive values indicate leftward asymmetries. Across the entire sample, significant leftward asymmetries were observed for the anterior insula ($t(198) = 8.07$, $p < .0001$), pars triangularis ($t(198) = 2.79$, $p < .01$), pars opercularis ($t(198) = 10.41$, $p < .0001$), and planum temporale ($t(198) = 11.41$, $p < .0001$). A small, but reliable, rightward asymmetry was observed for the posterior insula ($t(198) = -2.43$, $p < .05$). Consistent and mixed handers did not differ in degree of asymmetry for any of the five areas (all t-values <1). Fig. 2 displays the distribution of anterior insula asymmetries in our sample.
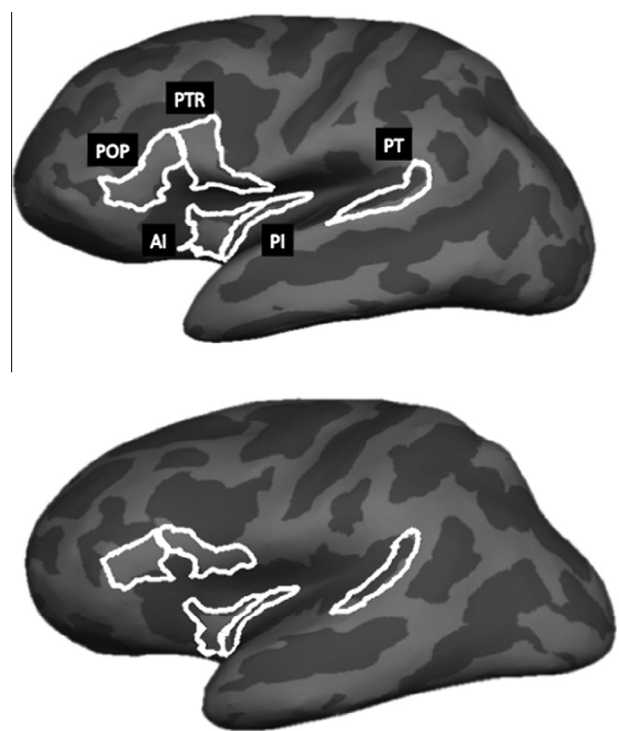

Fig. 1. Examples of FreeSurfer surface area renderings (left hemispheres) for two participants for the five parcellations of interest: pars opercularis (POP), pars triangularis (PTR), anterior insula (AI), posterior insula (PI), planum temporale (PT). Upper panel is from a mixed handed male; lower panel is from a consistent handed female.

Table 1
Mean (standard deviation) of surface area asymmetries for entire sample ($N = 200$) and by consistency of hand preference. Asymmetries that were significantly different from zero are noted via asterisks.

	Entire sample	Consistent handers ($N = 103$)	Mixed handers ($N = 97$)
Anterior insula	.09[***]	.09[***]	.09[***]
	(.16)	(.15)	(.16)
Posterior insula	−.03[*]	−.04[*]	−.02
	(.18)	(.18)	(.17)
Pars triangularis	.04[**]	.06[*]	.03
	(.22)	(.24)	(.21)
Pars opercularis	.13[***]	.14[***]	.12[***]
	(.17)	(.18)	(.17)
Planum temporale	.18[***]	.17[***]	.18[***]
	(.22)	(.21)	(.23)

[***] $p < .0001$.
[**] $p < .01$.
[*] $p < .05$.

Asymmetries for the five areas were generally uncorrelated. However, there was a small positive correlation between anterior insula and pars opercularis asymmetries ($r = .19$, $p < .01$). This correlation was significant for the consistent handers ($r = .21$, $p < .05$), but not for the mixed handers ($r = .17$, $p < .10$).

Hence, leftward surface area asymmetries were found for frontal and temporal language regions, and for the anterior but not the posterior insula, and these asymmetries were comparable for those with differing degrees of hand preference.

3.2. Structural/behavioral asymmetry associations

3.2.1. Divided visual field findings
RVF/left hemisphere advantages were obtained for all tasks (see Chiarello, Welcome, Halderman, & Leonard, 2009, Chiarello, Wel-
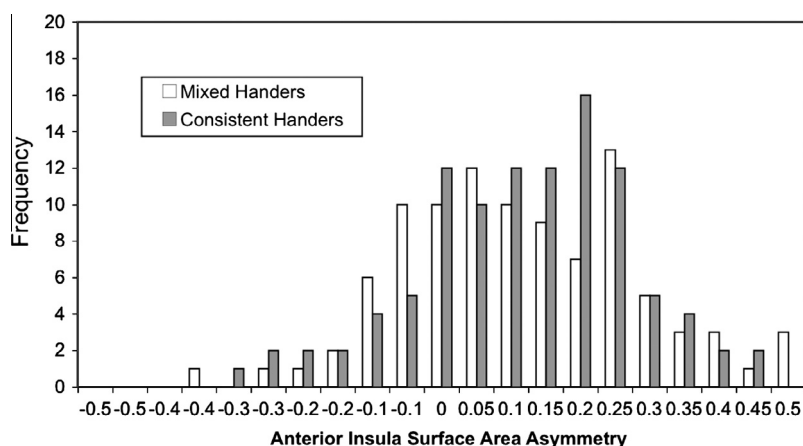
Fig. 2. Distribution of anterior insula asymmetry for mixed and consistent handers. Positive values indicate a leftward asymmetry.

Table 2
Correlation of surface area asymmetries with composite divided visual field asymmetry for entire sample ($N = 200$) and by consistency of hand preference.

	Entire sample	Consistent handers ($N = 103$)	Mixed handers ($N = 97$)
Anterior insula	.22[*]	.35[**]	.08
Posterior insula	.05	.10	−.02
Pars triangularis	.01	.04	−.05
Pars opercularis	.02	.03	.00
Planum temporale	.02	.08	−.05

[**] $p < .0005$.
[*] $p < .01$.

come, Halderman, Towler, et al., 2009). Because the composite asymmetry measure is based on an average across z-scores, participants with positive scores will have above average left hemisphere advantages, those with negative scores will have smaller left hemisphere advantages. There was no significant difference in mean composite asymmetry score between consistent (.04) and mixed (−.05) handers, $t(198) = 1.14$, $p = .26$. Table 2 includes the correlation coefficients for the association between anatomical and behavioral asymmetry for the entire sample, and each handedness group (see also Suppl. Table 2). Only the anterior insula asymmetry was related to the composite word reading asymmetry ($r = .22$, $p < .01$): those with greater leftward anterior insula asymmetries also tended to have greater RVF/left hemisphere word reading advantages. However, this association was entirely attributable to those with consistent hand preferences (consistent handers $r = .35$, $p < .0005$; mixed handers $r = .08$, $p = .45$). In contrast, asymmetries of the posterior insula and frontal and temporal language regions were not related to visual field asymmetry, for either hand group. This confirms the prior findings of Keller et al. (2011) that insula asymmetry uniquely predicts functional language asymmetry, but additionally localizes the association to more anterior insula regions.[3]

It might be argued that the lack of a significant structure/behavior correlation for the mixed handers is attributable to the larger number of left-handers in this group. Fig. 3 shows scatterplots

for the anterior insula findings with left-handed individuals indicated by filled circles. It does not appear that the left-handed participants had different structure/behavior associations for either the mixed or consistent hand group. This was confirmed by correlational analyses separating left- and right-handers for each hand strength group (left handers had hand preference scores <−.20). The anterior insula/composite asymmetry association was similar in magnitude for consistent handers, regardless of direction of handedness (right handers $r = .35$, $p < .005$; left handers[4] $r = .43$, ns). The correlations for mixed handers were likewise similar (right handers $r = .07$, ns; left handers $r = .11$, ns). These findings were not altered when the cut-off hand preference score for left-handedness was varied (<0; <+.30).[5]

Because the mixed and consistent hand groups had somewhat unequal sex distributions, and brain volume may have different predictive value for each hand group (Chiarello et al., 2008), we also included sex and intracranial volume (ICV) with anterior insula asymmetry as predictor variables in simultaneous multiple regressions. For mixed handers, none of the variables predicted composite asymmetry (t's < 1). For consistent handers, anterior insula asymmetry remained as a significant predictor, $t(102) = 4.06$, $p < .0001$, accounting for 13.5% of the variance. ICV was also a significant predictor, $t(102) = 2.18$, $p < .05$, accounting for 3.9% of variance. There was no effect of sex, $t < 1$. Hence, the relation between structural and behavioral asymmetry was unchanged when partialing out the effects of sex and brain volume.

Finally, because there is variation in degree and direction of handedness for the mixed handed group, we examined handedness as a continuous variable in another multiple regression for this group. Because some mixed handers have definite, but not extreme right hand preference, and others have less hand preference, it is possible that degree of handedness could moderate the anterior insula/composite asymmetry association. However, hand preference score did not account for significant variance for this relationship ($t < 1$), and indeed there was still no insula/composite asymmetry association for the mixed handers when handedness was treated

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[3] We also computed surface area asymmetry across the entire insula and correlated this with the composite VF asymmetry. Reliable correlations were obtained for the entire sample ($r = .20$, $p < .005$) and for consistent handers ($r = .32$, $p < .001$), but not for mixed handers ($r = .06$, ns). Because there is greater surface area for anterior (434 mm^2 left; 397 mm^2 right), than for posterior (312 mm^2 left; 321 mm^2 right), insula, associations observed with the anterior insula remain when total insular area is considered.

[4] There were only five consistent left-handers, so this coefficient should be interpreted very cautiously.

[5] We also explored a different way to identify consistent handers, similar to that used by Witelson (1989). According to this procedure, consistent right-handers are those who do not endorse any use of the left hand, even if they do not profess the strongest right hand preference ($N = 137$ in our sample). We re-ran the critical anterior insula/composite VF asymmetry correlation on this subset of our sample. A significant correlation was still obtained ($r = +.28$, $p < .002$), although it was smaller than that obtained using our classification of consistent handers. This suggests that adding individuals with consistent, but less strong, right hand preferences dilutes the effect we obtained using our classification of consistent handedness.
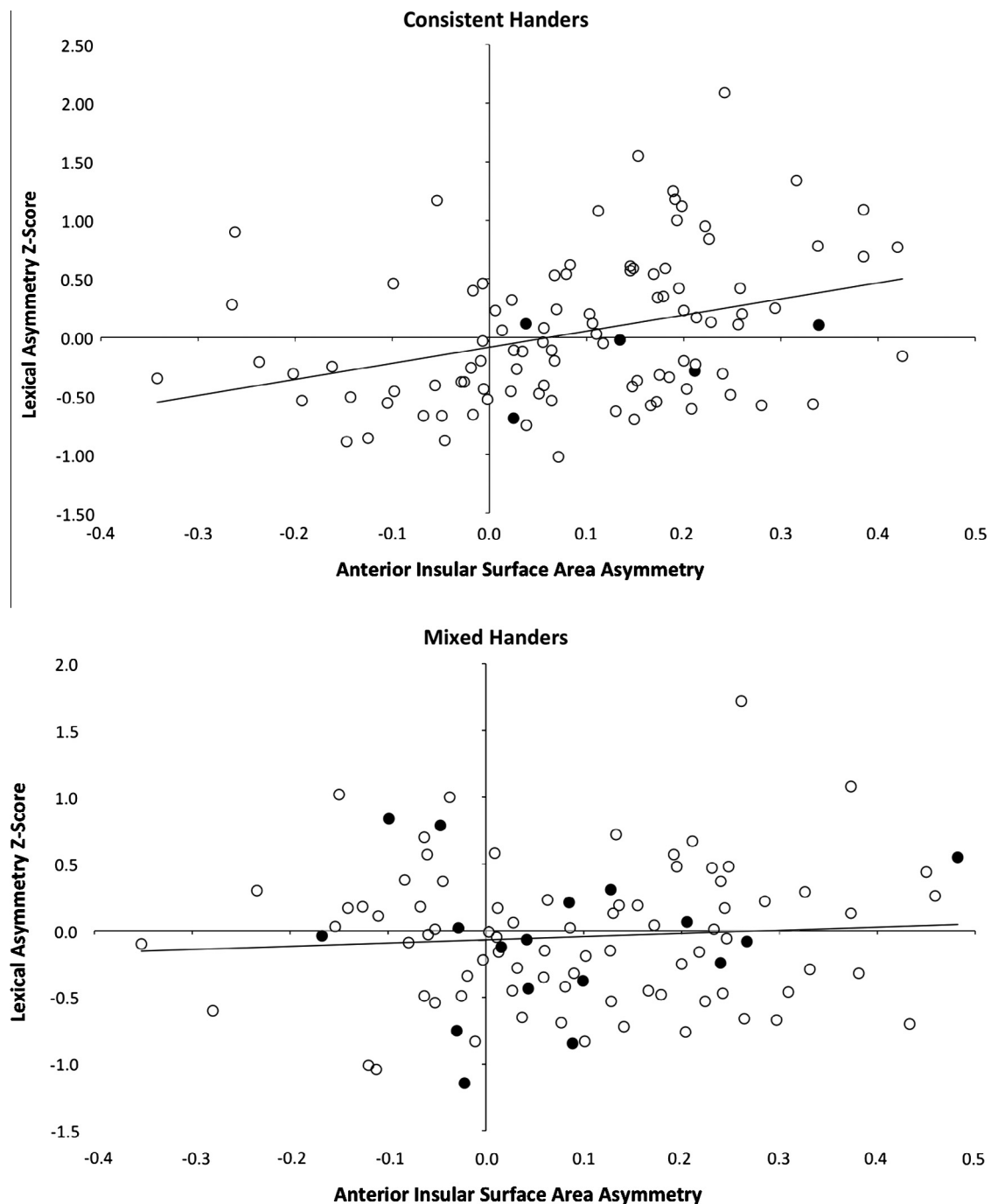
Fig. 3. Correlation of anterior insula surface area asymmetry with lexical asymmetry *z*-score for consistent handers (upper panel) and mixed handers (lower panel). Left-handers are indicated by closed circles.

as a predictor variable ($t < 1$). This result provides some support for treating mixed/consistent handedness as a categorical, rather than a continuous, variable.

3.2.2. Reading skill findings

We also examined correlations between cortical asymmetries and scaled scores from the three WRMT-R reading subtests (Word Identification, Word Attack, Passage Comprehension). For the posterior insula and pars triangularis, no relationship was observed with any reading measure. There was likewise no association of Passage Comprehension and asymmetry for any of the five regions. However, for both surface area (Table 3) and volume (Suppl. Table 3) word reading scores were associated with asymmetry of

the anterior insula, pars opercularis, and planum temporale. Planar asymmetries were positively correlated with reading scores across the entire sample, and for each separate hand group: better reading was consistently associated with more leftward planar asymmetries. Overall, there was a negative association of anterior insula asymmetry and word reading, but this relationship was significant only for mixed handers. For this group, greater leftward anterior insula asymmetry was associated with poorer word identification and word attack scores. These relationships for mixed handers were observed regardless of handedness direction (right handers $r = -.37$ and $r = -.20$ for word identification and word attack, respectively; left handers $r = -.20$ and $r = -.21$). In contrast, pars opercularis asymmetry was positively correlated with word

Table 3
Correlation coefficients of surface area asymmetry with reading subtest scores for entire sample ($N = 200$) and by consistency of hand preference.

	Entire sample	Consistent handers ($N = 103$)	Mixed handers ($N = 97$)
Word identification			
Anterior insula	−.24[***]	−.14	−.36[***]
Pars opercularis	.05	.21[*]	−.14
Planum temporale	.22[**]	.24[*]	.21[*]
Word attack			
Anterior insula	−.06	.09	−.21[*]
Pars opercularis	−.04	−.06	−.01
Planum temporale	.28[***]	.26[**]	.31[**]

[***] $p < .001$.
[**] $p < .01$.
[*] $p < .05$.

identification, but only for consistent handers (consistent right $r = .21$, consistent left[4] $r = .68$). Hence, asymmetry/reading correlations differed with strength of handedness for anterior, but not posterior, regions.

As for the divided visual field data, we also undertook multiple regression analyses to explore whether the reading score-brain asymmetry correlations were affected by sex or intracranial volume. Neither variable had an effect for the consistent handers, for any brain region. For mixed handers, neither sex nor ICV had an effect on the correlations with word attack. For word identification, anterior insula asymmetry remained a significant predictor, $t(96) = −3.45$, $p < .001$, accounting for 10.3% of the variance, and ICV was also a predictor, $t(96) = 1.97$, $p = .05$ (3.3% of variance). The effect of planum temporale asymmetry on word identification for mixed handers became marginally significant in the regression analysis, $t(96) = 1.89$, p = .06, and ICV was a reliable predictor $t(96) = 2.68$, $p < .01$ (6.7% of variance). In general, then, although brain volume is positively correlated with word reading among mixed handers, anterior insula asymmetry/reading correlations are still observed when potentially confounding variables were statistically controlled.

4. Discussion

4.1. Summary of major findings

Several important findings were obtained in this investigation. First, reliable leftward asymmetries were obtained from a large unselected sample of college students for the anterior insula, pars opercularis and triangularis, and planum temporale. These asymmetries were most robust for cortical surface area, but were also obtained for volume, which replicates and extends the prior findings of Keller et al. (2011). Since the anterior insula asymmetry was not observed for thickness (Suppl. Table 1), this indicates that volume asymmetry for this region is due to greater left hemisphere surface area. The anterior insula asymmetry was weakly correlated with pars opercularis asymmetry, but not with planar asymmetry, which parallels the greater structural connectivity between the anterior insula and frontal language regions (Cerliani et al., 2012). We also observed a slight, but reliable, rightward asymmetry for the posterior insula, a finding that has not been previously reported. Good et al. (2001) and Van Essen et al. (2012) found that a narrow slice of the posterior insula adjacent to Heschl's gyrus and the planum temporale had a leftward asymmetry. These differing findings may reflect differences in how the boundaries between regions are determined, as both Heschl's gyrus and the planum temporale typically display leftward asymmetry (Chiarello, Welcome, Halderman, Towler, et al., 2009; Dorsaint-Pierre et al., 2006).

Nevertheless our findings suggest that the anterior-posterior insular differences observed for connectivity and functional activation (Cerliani et al., 2012; Cloutman et al., 2012; Nieuwenhuys, 2012) may extend to differences in structural cortical asymmetry.

Second, anatomical asymmetries did not differ between individuals with strong, consistent hand preferences and those with weaker or inconsistent hand preference. This replicates prior findings using manual measurements of cortical asymmetry (Chiarello et al., 2007) and provides additional evidence that behavioral differences between these groups (e.g., Propper et al., 2005; Sontam et al., 2009) cannot be attributed to differences in structural brain organization (Chiarello et al., 2007; Welcome et al., 2009).

Third, we observed a positive association between anterior insula asymmetry and VF asymmetry for lateralized word reading tasks. Greater leftward asymmetry of the anterior insula predicted the degree of left hemisphere advantage for these tasks, whereas no such relationship was observed for asymmetry of inferior frontal and superior temporal language regions. This finding also extends the prior results of Keller et al. (2011) to a much larger and more representative sample, and to additional language tasks. The similarity between the current findings and those of Keller et al. (2011) is remarkable considering that the two studies employed very different methods for assessing cortical asymmetry and for measuring language lateralization. Both results imply a tighter coupling between structural and functional lateralization for the insula than for traditional language regions. We will consider the implications of such findings further below. We note, however, that the current results implicate primarily the anterior region of the insula, whereas Keller et al. (2011) did not utilize any structural landmarks to separately assess structure/function associations for anterior and posterior insular sulci. The current finding comports with a variety of functional imaging research that localizes activation for cognitive and linguistic tasks to more anterior regions of the insula (Kurth et al., 2010).

Fourth, several findings suggest that relationships between structural asymmetry and behavior differ for consistent versus mixed handers. Individuals with very strong hand preferences showed robust relationships between anterior insula asymmetry and language lateralization as measured by our divided visual field tasks. Yet although mixed handers have leftward cortical asymmetry that is comparable to that of consistent handers, their structural asymmetry was unrelated to VF asymmetry. However, structural asymmetries in several brain regions were associated with nonlateralized reading measures for mixed handers, which rules out interpretations that brain asymmetries for this group have no predictive value. These findings are discussed further below.

4.2. Limitations

Before considering the wider implications of the current study, its limitations should be noted. Our sample was unselected for handedness in order to represent the normal range of manual asymmetry present in the population. Hence, the number of left-handers, particularly consistent left-handers, was small. Although the mixed/consistent handed differences we obtained appeared to characterize both left- and right-handers, a sample that includes a larger number of left-handers will be needed to demonstrate this conclusively. In addition, our method for assessing lateralized language processing was based on divided visual field asymmetries and should be replicated using functional neuroimaging. However, we note that our major results align with the functional imaging findings of Keller et al. (2011) suggesting that the correlations we obtained are not limited to a single method of assessing lateralized processing.

Our neuroanatomical methods also require comment. We relied on fully automated methods to parcellate the insular cortex. Such

methods have the advantage in being reproducible, amenable to large sample sizes, and more readily facilitate comparisons across laboratories and differing samples than do manual measurement techniques. However, such methods cannot supplant manual measurements by skilled neuroanatomists who can determine boundaries based on subtle individual differences in cortical anatomy that might be missed using automated procedures. In addition, the parcellation of anterior and posterior insula was based on a discrete sulcal boundary, but other divisions of the insula may be more informative. For example, both connectivity and functional data suggest a gradual posterior to anterior shift in the organization of the human insula. The existence of a central transitional zone between anterior and posterior insular regions has been identified (Cerliani et al., 2012; Cloutman et al., 2012), but structure/ function relationships for this area cannot be determined using the method we employed. The areal parcellations we utilized also did not differentiate between more dorsal and ventral regions of the anterior insula. Yet prior research would suggest that the structure/behavior relationships we obtained should be stronger for dorsal, than for ventral, portions of the anterior insula (Kurth et al., 2010; Nieuwenhuys, 2012). Cohen et al. (2010) present a method to divide the insula into anteroventral and posterodorsal regions that approximate transitions in cytoarchitecture and connectivity. It will be important in future studies to assess the generality of our findings by employing multiple techniques to partition the insula, and comparing functional correlations for each partition method.

4.3. Asymmetry of classical language areas

Although our most important findings concern asymmetry of the insula, our data also speak to the issue of structural asymmetries of classical language regions and their functional significance. Leftward asymmetry of the planum temporale is a robust finding in the literature (Shapleske, Rossell, Woodruff, & David, 1999). Our results for both surface area and volume provide an additional replication, and further demonstrate that planar asymmetry does not vary with strength of handedness. The relationship of planar asymmetry to functional language lateralization is less clear. In small or select samples, occasional positive structure–function correlations have also been reported (Chiarello et al., 2004; Foundas, Leonard, Gilmore, Fennell, & Heilman, 1994). However, in the current investigation we did not find any correlation of planum temporale asymmetry with our lexical asymmetry measure, and attempts to correlate planar asymmetry with fMRI or Wada test measures of language lateralization have been largely unsuccessful (e.g., Dorsaint-Pierre et al., 2006; Eckert et al., 2006; Jansen et al., 2010; Keller et al., 2011).

Although structural asymmetry of the planum temporale is well established, asymmetry of Broca's region is more uncertain. A recent thorough review noted that morphological asymmetry of this region (pars opercularis and triangularis) is quite variable and difficult to replicate (Keller, Crow, Foudas, Amunts, & Roberts, 2009). The findings reported here only partially support this conclusion. Leftward asymmetry of pars opercularis was very robust for surface area and volume in the current sample, whereas leftward asymmetry of pars triangularis was smaller in magnitude and more variable for surface area, and absent for volume, measurements (see Table 1 and Supplementary Table 1). Because the MRI studies cited by Keller et al. (2009) utilized either manual tracing or stereology measurements, one might wonder whether the current findings reflect some idiosyncracy of the FreeSurfer parcellation methods. However, manual measurements of inferior frontal asymmetry with the current sample yielded similar results: highly significant leftward asymmetry of pars opercularis for both males and females, but much more variable asymmetry of pars triangu-

laris that only barely reached significance for females but not males (Chiarello, Welcome, Halderman, Towler, et al., 2009 – see their Table 1). Keller et al. (2009) did report that studies that measured the entire surface of the inferior frontal gyrus found leftward asymmetry of the pars opercularis but not triangularis, but also noted that these findings were difficult to replicate. The method employed here also measures the entire gyral surface, but in a significantly larger sample than in prior studies. Given the not infrequent failures to replicate structural asymmetry of Broca's region, we do not wish to over-interpret the current pars opercularis findings. However, this is a research area that would benefit from a formal meta-analysis and/or a replication with a new large sample. Furthermore, although we did observe reliable opercular asymmetries, there was no correlation with our lexical asymmetry measure. Hence the functional significance of this frontal asymmetry remains uncertain.

4.4. Relationship of surface area and thickness asymmetries

Hogstrom, Westlye, Walhovd, and Fjell (in press) have recently suggested that biologically meaningful information can be obtained by examining the association between cortical surface area and thickness. Comparison of the surface area asymmetries reported in Table 1, and the volume and thickness asymmetries found in Supplementary Table 1, reveal two incidental findings that may be of interest for future investigations. First, for the traditional inferior frontal and superior temporal language areas, the left hemisphere has greater surface area and volume, but thinner cortex, relative to the right hemisphere. This result is consistent with Hogstrom et al.'s (in press) finding of negative correlations between surface area and thickness that remain stable across the lifespan. Hogstrom et al. (in press) attribute this relationship to pre-adult neurodevelopmental events during which early growth of white matter stretches adjacent gray matter. They further note that this relationship reflects a phylogenetic principle that maximizes surface area, but not thickness, to enhance connectivity and functional development. Our asymmetry findings for language-relevant cortex suggest that such processes are potentiated in left hemisphere areas important for language function.

Second, different cortical features characterize anterior versus posterior insular asymmetries. Leftward asymmetry of the anterior insula was attributable to greater surface area with no concomitant difference in cortical thickness, while rightward asymmetry of the posterior insula was attributable to greater surface area coupled with increased cortical thickness. According to the logic of Hogstrom et al. (in press), this could indicate reduced selective pressure on posterior, relative to anterior, insular cortex. Although we cannot speculate further on the mechanisms that may have produced these hemispheric differences, such findings document an additional anatomical substrate that may underlie anterior/posterior differences in insular function.

4.5. Asymmetry/behavior associations in consistent versus mixed handers

Anterior insula asymmetry predicted lateralized language processing only in individuals with strong, consistent hand preferences. This suggests that in consistent handed individuals the developmental factors that induce cortical asymmetry in the anterior insula modulate functional language lateralization as well (this suggestion will be discussed further below). It also implies that for persons with weak or inconsistent hand preferences, there are influences beyond structural asymmetries that affect functional language lateralization. If mixed handers do have greater interhemispheric communication during language processing (Christman et al., 2004, 2008), then perhaps cortical asymmetries would

have less influence on behavioral outcomes. However, the interhemispheric hypothesis would also predict reduced VF asymmetries for mixed handers, yet our findings do not support this prediction. Clearly, additional research will be needed to more fully understand lateral brain organization of mixed handers.

For both handedness groups, there was a positive association between planum temporale asymmetry and standardized word and nonword reading measures. Prior findings about the relation between planar asymmetry and reading skill have been mixed (Eckert & Leonard, 2000; Welcome, Leonard, & Chiarello, 2010). However, our large sample of typical readers documents a small but reliable association suggesting that greater leftward surface area asymmetry contributes to better word reading. More important for the current investigation, however, is the finding of hand group differences in word reading correlations for anterior (anterior insula, pars opercularis), but not posterior (planar), asymmetries. Among mixed handers only, word and nonword reading was negatively associated with anterior insula asymmetry – better reading for this group was associated with reduced asymmetry. In contrast, for consistent handers only pars opercularis asymmetry was positively associated with word identification. These data suggest that skilled reading may be supported by a different type of brain organization for mixed and consistent handers. Among consistent handers better reading is associated with greater leftward asymmetry for frontal and temporal language regions. For mixed handers, better reading is associated with greater brain volume (see multiple regression results), greater leftward planar asymmetry, but reduced leftward anterior insula asymmetry. That hand group differences were only observed for anterior regions suggests that the expression of handedness strength may be just one indication of differing structure/function relationships in frontal areas. We know of no prior study investigating the role of degree of handedness on structural correlates of reading, but our findings imply that this may be a critical moderating variable.

4.6. Theoretical interpretations

Perhaps the central question raised by our findings is "Why the insula?" We documented leftward structural asymmetries across several language relevant cortical regions, but only the anterior insula asymmetry predicted asymmetry of language processing. Although the anterior insula is often activated in language tasks, it cannot be argued that this region is more important for language processing than left inferior frontal, superior temporal/parietal, or middle temporal regions (Price, 2010, 2012). The answer we offer to the above question is conjectural, but we suggest that an ontogenetic approach may be fruitful.

Evidence suggests that the insula is the first cortical region to differentiate and mature (Afif, Bouvier, Buenerd, Trouillas, & Mertens, 2007; Wai et al., 2008). This implies that at the earliest stages of language acquisition the insular cortex may be functionally more mature than frontal and temporoparietal language areas. In addition, young children appear to make greater use of the ventral extreme capsule pathway (mediating connections between insular and language-relevant cortex) for language relative to adults (Brauer, Anwander, & Friederici, 2011). A consideration of early language acquisition reveals potential links to anterior insula functions. Language emerges in infancy and early childhood in a social-emotional context in which the quality of caregiver interactions, both verbal and nonverbal, may play a particularly important role (Tamis-Lemonda, Bornstein, & Baumwell, 2001). For example, during the babbling stage contingent social feedback from caregivers induces infant vocalizations with more advanced phonological features and can actively shape their phonological structure (Goldstein, King, & West, 2003; Goldstein & Schwade, 2008). As noted by Goldstein et al. (2003), such findings imply that neural structures involved in the acquisition of speech production must be sensitive to nonauditory forms of social feedback. Nine- to ten-month old infants acquire language-specific phonetic perception for a foreign language only when exposure occurs in the context of social interaction (Kuhl, Tsao, & Liu, 2003). Furthermore, word learning prior to age 2 years seems to require an interacting social partner; on-screen media exposure is insufficient (Richert, Robb, & Smith, 2011). Joint attention between infants and caregivers is also a critical component of early communicative interactions and is predictive of subsequent language learning (Farrant, Maybery, & Fletcher, 2011; Silven, 2001; Tomasello, 2007). We earlier cited findings that implicated the anterior insula in social emotions and interaction, salience detection, the control of attention, and speech production (Dronkers, 1996; Guionnet et al., 2012; Lamm & Singer, 2010; Menon & Uddin, 2010). Thus we suggest that anterior insula asymmetry may be particularly important for the establishment of functional language lateralization because the anterior insula provides a critical substrate for cross domain linkages that are necessary for the early stages of language learning. Because this brain region is uniquely situated to integrate across multiple domains (Kurth et al., 2010) including social, emotional and attentional systems, it may be crucial for the emergence of social communication and speech. Hence, leftward structural lateralization of earlier developing insular cortex may bootstrap asymmetrical functional lateralization even if the insula is only a minor component of the adult language network.

Additionally, the left anterior insula may continue to play a role in some aspects of language learning across the lifespan. Some evidence suggests that this brain region plays a role in phonological and grammar acquisition even in adulthood. For example, left insular activation in speech production tasks may be enhanced when production of foreign or unfamiliar speech sounds is required (Moser et al., 2009; Shuster, 2009). Left anterior insular activation also increases when phonological working memory is engaged for words in an unfamiliar language, especially for individuals with better second language proficiency (Chee et al., 2004). In addition, effective connectivity analyses have identified the left insula as an important component of the network involved in explicit learning of artificial grammars among adults (Yang & Li, 2012). It has also been suggested that left anterior insular injury decreases the likelihood for functional recovery of speech after damage to other components of the left hemisphere language network (Moser et al., 2009). Hence normal functioning of this insular area may facilitate (re)learning of articulatory and/or grammatical sequences.

4.7. Conclusions and further directions

The current findings and our provisional interpretations suggest some important avenues for future research. It will be important to determine when structural and functional asymmetry of the anterior insula emerges relative to asymmetry in more traditional language regions. Our hypothesis predicts that insula asymmetry should be established earlier in development. It will also be useful to investigate the extent to which the leftward surface area asymmetry is associated with asymmetry of the underlying white matter. Finally, our findings suggest that strength of hand preference is an important contributor to individual differences in structure/function relations, and should be considered in clinical investigations of language dysfunction. Our findings imply that the functional outcome of at least some left hemisphere lesions may differ between mixed and consistent handers. Future studies should report and investigate the correlates of degree, and not just direction, of handedness.

In conclusion, the current data document leftward structural asymmetry of the anterior insula, and suggest that this asymmetry

correlates with language lateralization in individuals with strong, consistent hand preferences. These findings contribute to an emerging consensus that the anterior insula is an important component of numerous functional networks, including those involved with language processing.

Acknowledgments

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandl.2013. 03.005.

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