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Sex-linked Variation in Anterior Cingulate Morphology & Electrophysiology

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Abstract

Sex differences in cognition and the differential susceptibility of men and women to various psychiatric disorders may be partly explained by differences in structural characteristics of the brain present from birth. One such characteristic may be the pattern of gyrification on the cortex. While the presence and location of sulci are largely genetically pre-specified, there is reason to believe prenatal androgen exposure may influence this process in a regional specific way. Gyrification of the left anterior cingulate cortex (ACC) is particularly interesting as it shows high variability across individuals, has been found to be sexually dimorphic and appears to be correlated with electrophysiological and behavioral markers in executive tasks. In this study, we test the inter-relationships between sex, a putative marker of prenatal androgens (the 2D:4D finger ratio) gyrification asymmetry across the ACC and task-related electrophysiological marker believed to be generated in the ACC: the N2.

Keywords: N2, sex, gender, prenatal hormones, ACC, gyrification, asymmetry, 2D:4D ratio

Introduction

The chances of developing certain psychological disorders are different for males and females. Also, the presentation of symptoms— age of onset, symptom severity and range of comorbidities— often show sex differences. Such effects have become apparent in Autism Spectrum Disorders, depression, Alzheimer's disease, PTSD, schizophrenia, stroke, multiple sclerosis, addiction and Tourette's syndrome (see Cahill, 2006 for a review). Unsurprisingly, it is sometimes noted that males and females respond differently to pharmacological treatments (e.g. depression: Kornstein et al., 2000; ADHD: Marchant et al., 2011) but unfortunately this is often reported following treatment approval, or if discovered during clinical trials remains an unexplored covariate (Fadiran & Zhang, 2015; Johnson, Fitzgerald, Salganicoff, Wood & Goldstein, 2014).

Abnormalities in frontally-mediated executive functions are a key feature of many of the disorders mentioned above, however research on executive functioning in neurologically normal samples has not reached any conclusions for or against the presence of sex differences. Some studies find sex differences in inhibitory control (Kessler, 2005; Lipsyc & Schachar, 2010; Hooper et al., 2004; Hansen, 2011) while others fail to (Evans & Hampson, 2015; Li et al., 2006, 2009). Similarly, inconsistent findings obscure the link between gender and other executive functions like selective attention (Christakou et al., 2009; Stoet, 2016; Evans & Hampson, 2015) and task-switching (Stoet, Connor, Conner & Laws, 2013; Buser & Peter, 2012).

To better understand how sex relates to executive functioning, it is important to acknowledge the multi-faceted nature of both variables. Executive functions encompass a range of distinct cognitive processes and rely on the interplay of a range of subcortical and frontal regions (Alvarez & Emory, 2006; Seeley et al., 2007). It may be that sex influences the functioning of these distinct subcomponents, or functional "nodes", in different ways, resulting in a sex-linked bias

toward one neural strategy over another. In this thesis, we attempt to tap individual differences in the recruitment of one important subcomponent of executive functioning: the dorsal anterior cingulate (dACC; Botvinick, Cohen & Carter, 2004; MacDonald, Cohen, Stenger & Carter, 2000). Further, delineating the factors which sexually differentiate the brain may help improve our understanding sex differences in the brain. While genetic factors can induce sex differences directly, many permanent sexual dimorphisms in the brain are the result of differential exposure to sex hormones in utero (Phoenix, Goy, Gerald &Young, 1959; Arnold, 2009). Virtually all neural and behavioral patterns are sex-typical, not sex-exclusive, thus a biological gradient which sexually differentiates the brain in a somewhat probabilistic fashion, such as prenatal sex hormones, may be a more appropriate correlate of sex-linked variation in brain structure and functionality than the sex dichotomy.

The aim of this study was to investigate whether prenatal hormone levels (as operationalised by the 2D:4D finger ratio) could explain sex-linked variation in gyrification patterns within the dACC. We chose to focus on dACC gyrification given previous reports of sexual dimorphism in its gyrification patterns (e.g. Leonard, Towler, Welcome & Chiarello, 2009) and structural connectivity (e.g. Huster, Westerhausen, Cruder, Schweiger & Wittling, 2009).

ACC Gyrification Patterns

There are two major sulci that can be found on the medial wall of the ACC: the cingulate sulcus (CS) and the paracingulate sulcus (PCS; Figure 1A). Despite ubiquity across neurologically-normal individuals regarding bilateral presence of the CS, there appears to be significant variation regarding the PCS, which is present in only 30–60% of individuals and more commonly found in the left hemisphere (Paus et al., 1996b; Watkins et al., 2001; Kennedy et al., 1998; Thompson et al., 1996; Fornito et al. 2008; Leonard et al., 2009).

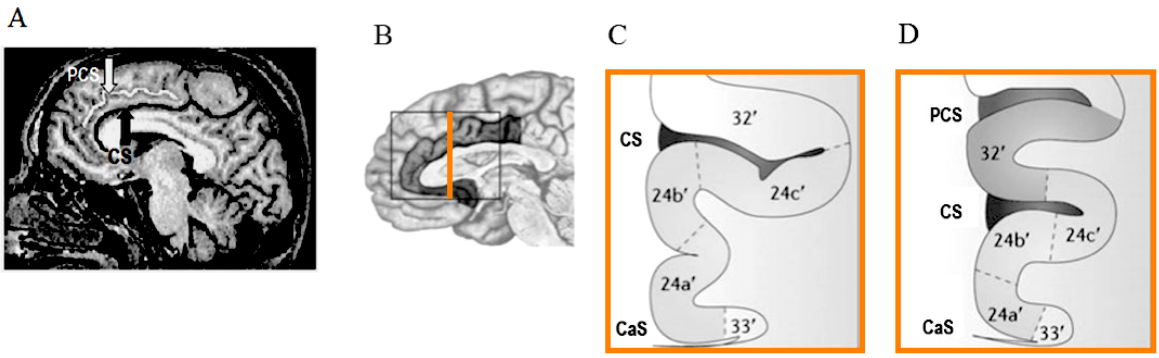

Figure 1. Gyrification patterns of the ACC. (A) shows the two major sulci of the ACC: the cingulate sulcus (CS) and the paracingulate sulcus (PCS). Individual differences in this area are often defined by PCS length. (B) Sagittal view indicating the slice position of the following images: (C) a cingulate with CS only, and (D) a cingulate with both CS and PCS (CaS: Callosal Sulcus. Numbers in C and D refer to Brodmann areas; images from Le Provost et al., 2003 and Shackman et al., 2011).

As shown in Figure 1D, the presence of a PCS affects not just the gross surface morphology of the area but also the relative size and locations of cytoarchitectural regions (Vogt et al., 1995). Furthermore, the consequences of this sulcal doubling in the ACC are not trivial and has been related to several indices of cognition, affect and behavior (Fornito et al., 2004, 2006b; Yücel et al., 2002b, c; Huster et al., 2009, 2011, 2014; Pujol et al., 2002).

Sex & ACC Gyrification Patterns

One interesting feature of the pattern of gyri and sulci on the cingulate is that unlike its volume and thickness, it does not change much after birth (Armstrong et al., 1995; White et al., 2010). In normally-developing fetuses, the CS starts to develop around week 18 and the PCS (when present), 10-15 weeks later (Chi, Dooling & Gilles, 1977; Garel et al., 2001). While the depth, length and course of these sulci do vary somewhat over childhood and adolescence, their qualitative presence does not (Armstrong, Schleicher, Omran, Curtis & Zilles, 1995; Pienaar, Fischl, Caviness, Makris & Grant, 2008) and regarding the ACC in particular, the presence of a single or double sulcal formation (Figure 1) appears to remain stable throughout childhood and adolescence (Cachia et al., 2016).

Given that hormone-induced sexual differentiation of the brain coincides with the development of the sulci (Phoenix et al., 1959; Arnold, 2009), one might question whether the resulting ACC sulcal pattern is influenced by such pressures. If so, one might expect sex differences in this pattern. Indeed, Yücel et al. (2001) and Huster et al. (2007) have found sex differences in the extent of ACC gyrification in the left vs. right hemisphere. Specifically, a leftward asymmetric pattern, as defined by longer PCS lengths in the left hemisphere compared to right, is more common in males than females (see Figure 2), though this distribution of the sexes across asymmetry types appears to be specific to right-handers (Huster et al., 2007).

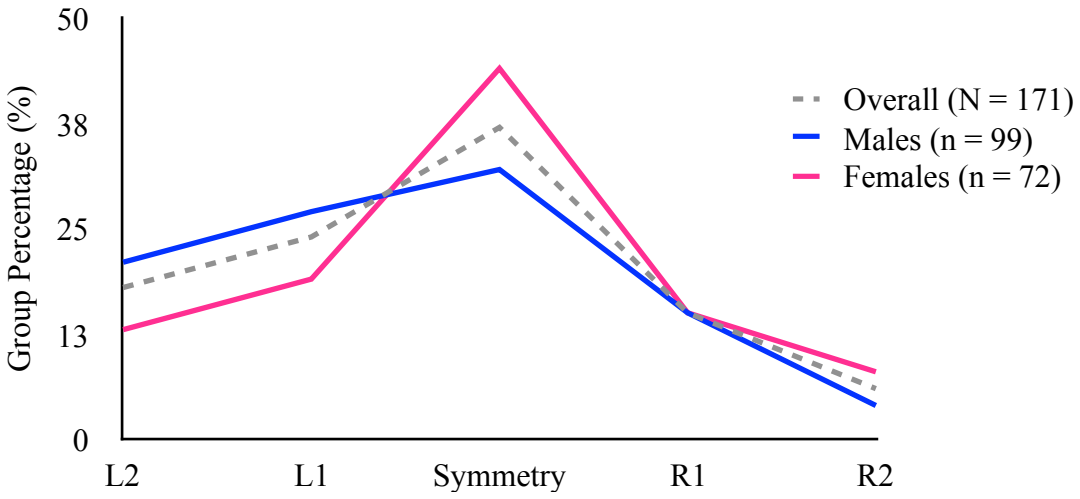

Figure 2. Distribution of a large sample ($N = 171$) across categories of ACC gyrification asymmetry. Five categories of PCS-asymmetry are shown: extreme asymmetries (L2/R2) were those in which the PCS was prominent in one hemisphere (in terms of its length) and absent in the other. Data from Yücel et al., 2001.

One problem with categorising ACC gyrification on the basis of PCS length (the standard since Paus et al.,1996a), is the difficulty in unambiguously dissociating the PCS from displaced CS segments (Leonard et al., 2009). Furthermore, given that PCS presence influences the position and relative size of surrounding cytoarchitectural regions (Paus et al., 1995) and sulci (Connolly et al.,

1940), it is unclear whether the functionally relevant feature (and that which shows a sex difference) is the asymmetry of PCS length, as has been implied by previous research, or one of these related side-effects. To avoid time-consuming manual tracings, misclassification of PCS/CS and to explore gyrification of the general region, we adopted an automated, curvature-based gyrification index and applied it to a region of interest, the dACC. This gyrification index has been shown to be sensitive to small-scale regional differences in gyrification (Luders et al., 2006).

Hypothesis 1

There will be a sex difference in ACC gyrification patterns such that males will exhibit greater gyrification within left dACC relative to their right dACC (greater leftward asymmetry)

Prenatal Sex Hormones & ACC Gyrification Patterns

The sex dichotomy can explain a limited portion of variance in cortical surface morphology and provides limited etiological information. Exposure to sex hormones (e.g. testosterone) in utero is a continuous variable that is believed to sexually differentiate the brain (Phoenix et al., 1959; Arnold, 2009) and there are several lines of evidence to suggest it influences gyrification of the ACC in an asymmetrical fashion.

First, Huster et al. (2007) found that sex differences in ACC gyrification patterns were driven by differences in the left hemisphere. This is interesting because left hemisphere development of grey matter volume has been found to be twice as susceptible to environmental influences as right hemisphere development (Geschwind et al., 2002). Second, the cingulate is a known high-density androgen-receptor region in rats (Nuñez et al., 2003) and rhesus monkeys (Clark et al., 1988; Sholl and Kim, 1990b). In fetal rhesus brains, androgen-receptor densities are

unequally distributed across the right and left cingulum in males, while no such asymmetry exists in females (Sholl and Kim, 1990a). Third, the cytoarchitectural patterning of the cortex and regional expansion which decide the presence and positioning of sulci (Ronan & Fletcher, 2014) coincides with the time in which gonadal hormone levels show maximal sex difference (mid-Trimester 1; Tapanainen et al., 1981; Finegan et al., 1989). Fourth, Lombardo et al. (2012) found a negative correlation between amniotic testosterone (measured between gestational weeks 13-20) and dACC volumes (BA 24), which tends to be strongly and positively correlated with gyrification (Gautam et al., 2015). Finally, Autism Spectrum Disorder (ASD) is often considered an expression of the extreme male brain (Baron-Cohen et al., 2005; 2011) and is associated with exposure to above-average levels of foetal testosterone (Baron-Cohen et al., 2014). Ecker et al. (2010) found that, the degree of folding in the ACC differentiated ASD cases from controls, with folding in the left hemisphere a more sensitive predictor (80%) of ASD than folding in the right (45%).

Despite this evidence, no study has tested the relationship between sex hormone exposure in utero and the extent of gyrification in the ACC. Our second hypothesis assumes a link between prenatal hormone levels and ACC gyrification asymmetry, but first we explain how prenatal hormone variation was approximated.

The 2D:4D finger ratio. The ratio between the length of the 2nd digit (the index finger) and the 4th (the ring finger) is a sexually dimorphic trait (Hönekopp & Watson, 2010) and is believed to reflect prenatal hormone levels such that higher concentrations of testosterone (relative to estradiol) relates to lower “male-typical” 2D:4D ratios. Several lines of evidence supporting the 2D:4D ratio’s construct validity are provided:

Testosterone measured directly from the amniotic fluid at around 16th gestational week correlates with the right-hand 2D:4D ratio in the same infants at 2 years old (Lutchmaya et al.,

2004). Androgen insensitivity syndrome involves the partial or complete insensitivity of the androgen receptor and thus the inability of cells to respond to androgens. Genetic males with this disorder develop many female phenotypical traits and have 2D:4D ratios that are significantly higher than then the male mean (Berenbaum, Bryk, Nowak, Quigley & Moffat, 2009). Another disorder, congenital adrenal hyperplasia, involves excessive androgen exposure prenatally and is associated with reduced 2D:4D ratios in both male and female patients compared to respective gender norms (Hönekopp & Watson, 2010). Experimentation with mice, which also display a sexually dimorphic 2D:4D in front paws, shows that the effect arises from the differential distribution of androgen and estrogen receptors across the digits, in conjunction with different levels of circulating testosterone and estradiol during cartilage development of the digits (Zheng & Cohn, 2011).

While some doubts exist regarding the construct validity of the 2D:4D (see Berenbaum et al., 2009), it is considered to be a suitable alternative to amniotic fluid testing given that this is the first investigation of the link between prenatal hormone exposure and the extent of cingulate gyrification (or indeed gyrification in any region). The results of this study may provide the impetus for future studies to test this link using more direct measures of foetal hormone levels.

Hypothesis 2

The 2D:4D finger ratio will be correlated with gyrification asymmetry in the ACC in a manner consistent with the predicted sex difference (low "male-typical" 2D:4D related to more leftward asymmetry).

Functional Relevance of ACC Gyrification Asymmetry

Earlier we mentioned that the prominence of the PCS, particularly in the left hemisphere, is

not trivial. It appears to have implications for executive abilities (Fornito et al., 2004, 2006b) and clinical disorders such as obsessive-compulsive disorder and schizophrenia (Fornito et al., 2008; Yücel et al., 2002b; Shim et al., 2009). The surface area of the anterior cingulate gyrus, a feature inversely related to PCS prominence (Paus et al., 1995), has been linked with the personality trait of harm avoidance, explaining a large portion of the sex difference on this trait (Pujol et al., 2002).

On a more fine-grained level of neurocognitive processing, the asymmetrical prominence of PCS in the left hemisphere has been related to variation in task-related modulations of the N2.

The N2. The N2 is an event-related potential (ERP) component which appears as a negative-going peak around 200ms post-stimulus, contingent on the probabilistic characteristics of the stimulus. Specifically, an N2 peak can be observed following relatively unexpected (low-probabilistic) stimuli (e.g Nieuwenhuis et al., 2003) however, the N2 also appears to be sensitive to response demands: greater N2 amplitudes are found in response to NoGo compared to Go stimuli, even when conditions have equal probabilities (Pfefferbaum, Ford, Weller & Kopell, 1985; Nieuwenhuis et al., 2003). The sensory-modality independence of these effects and the precedence of N2 amplification to up-regulation of attentional resources and improvements in cognitive control have led researchers to believe that the N2 reflects a generalised element of executive functioning described as conflict detection or conflict monitoring, thought to take place in the ACC (Botvinick et al., 2001, 2004; van Veen & Carter, 2006; Carter & van Veen, 2007; Forster et al., 2011). Concurrently, a range of source localisation methods have pointed to the ACC and adjacent medial frontal cortices as the source of the N2 (van Veen & Carter, 2002a,b; Bekker et al., 2005; Jonkman et al., 2007; Lamm, Zelazo & Lewis, 2006; Nieuwenhuis et al., 2003; Yeung et al., 2004; Ridderinkhof, Ullsperger, Crone & Nieuwenhuis, 2004).

The asymmetrical prominence of the PCS appears to be related to the extent of

differentiation between Go and NoGo/Stop N2 amplitudes (Huster, Enriquez-Geppert, Pantev & Bruchmann, 2014). Specifically, NoGo- and Stop-related N2 amplitudes were significantly more negative than Go-N2 amplitudes but only in those showing a leftward PCS asymmetry (Figure 3), that is, those with a prominent left PCS and no right PCS.

This leftward asymmetry has also been associated with stronger conditional differentiation of another frontocentral negative component, the Stroop N400 (Huster et al., 2009, 2014). In these Stroop tasks, having a leftward asymmetrical PCS was also associated with faster response times on incongruent Stroop trials and a larger congruency effects (incongruent accuracy < congruent accuracy) compared with those displaying rightward asymmetry or symmetry.

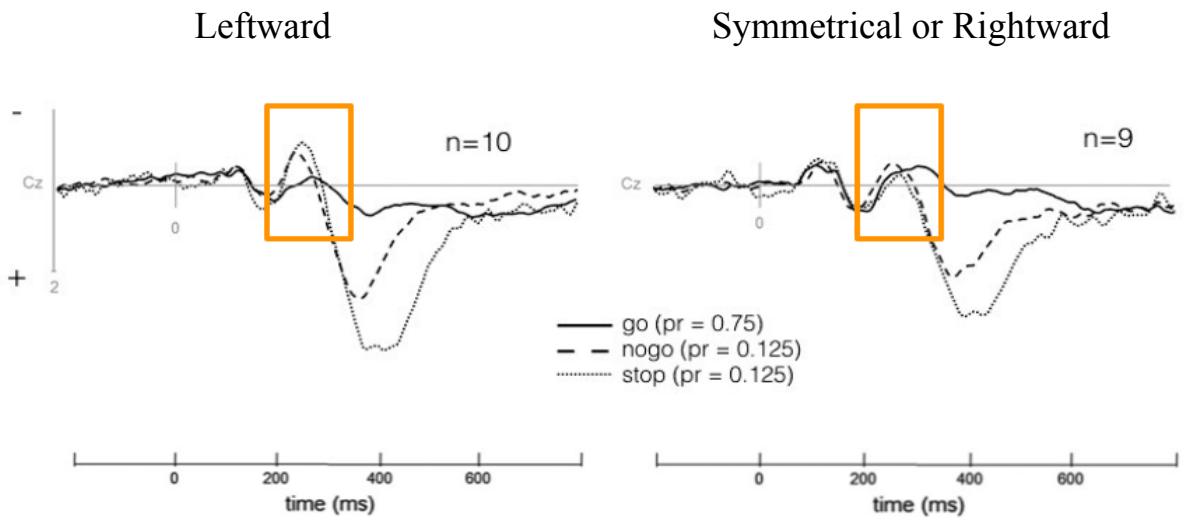

Figure 3. ERPs from a combined Go/NoSo and Stop-Signal task for the leftward asymmetry group vs. other ACC folding types. NoGo- and Stop-N2 amplitudes are greater in the leftward gyrification asymmetry group compared with the other group. From Huster et al. (2014, Study 2). pr = probability of trial-type.

Hypothesis 3

Leftward gyrification asymmetry within the dACC

will relate to greater conditional differentiation of N2 amplitudes.

Sex & The N2

We have now reviewed the evidence for sex differences in ACC sulcal asymmetry and for links between this asymmetry and N2 amplitudes— we turn now to the final link in the triad between sex and N2 amplitudes.

The existing evidence regarding the sex difference in N2 amplitudes is contradictory with some studies reporting a larger conflict-related N2 in males than female (Clayson et al., 2011; Omura & Kusumoto, 2015) and others reporting the opposite (Yuan et al., 2008). Furthermore, these studies vary the task used to induce the N2 (Flanker, AX-continuous performance, Oddball) and task parameters (stimulus durations and probabilities, uni- vs bi-lateral response options).

While state factors may influence the sex difference in N2 amplitudes, (e.g. menstrual hormones; Walpurger, Pietrowsky, Kirschbaum & Wolf, 2004), we speculate that sex-linked variation in a structural brain feature, ACC gyrification, may account for the sex difference in N2 amplitudes. In our final hypothesis we thus predict that sex differences in the N2 will align with sex differences in ACC gyrification asymmetry in a way that is consistent with the structure-function links discussed.

Hypothesis 4

There will be a sex difference in N2 amplitudes such that the sex with greater leftward gyrification asymmetry will exhibit greater differentiation of Go and NoGo-N2 amplitudes.

Method

Participants

Participants were recruited through posters in the Department of Psychology (University of Oslo) and social media groups. Screening occurred via a phone-call and participants were excluded

if they were outside the 18-35 year age bracket, were left-handed or had a history of psychiatric or neurological illness. Due to the difficulties posed to EEG preparation, individuals with dreadlocks or an afro hairstyle were excluded. MRI safety protocol excluded participants with metal body-implants, metal dental-implants (e.g. braces), recent tattoos or irremovable piercings. Participants were also excluded if they suffered from claustrophobia or were pregnant.

The screened sample consisted of 37 individuals (20 females, 17 males). Ages ranged from 19 to 35 ($M = 26.81$, $SD = 5.37$) and did not differ significantly between men and women. The sample was composed of 17 nationalities, the main contributors of which were Norwegian, German and Estonian. All participants completed the EEG session. Two males did not attend the MRI session due to scheduling problems and another male did not provide a left 2D:4D ratio due to a hand injury. Participants were included in all analyses that did not include variables for which they had missing data.

Participants were removed from EEG analysis if their behavioral performance indicated that task instructions were not understood or task engagement was excessively poor. This was defined as a Go or NoGo accuracy score below 85%. Based on this criteria, 1 female was removed (Go accuracy = 83.8%).

Procedure

Participants attended two testing sessions, one including 2D:4D measurement, EEG and behavioral testing (~3 hours) and the other for MRI scanning (~ 30 mins). Participants provided written informed consent and completed the Edinburgh Handedness Inventory (Oldfield, 1971) to validate self-reported right-handedness. During EEG acquisition, participants performed a Go/ NoGo and a Stop-signal task, and the order in which they were performed was counterbalanced

across participants.

Measures

2D:4D finger ratios. High resolution (400 dpi, 48-bit) images of the ventral side (palm) of both hands were obtained with an Epson Perfection V370 scanner and saved as PDF files with participant ID. No other identifying information was visible from the image (e.g. clothing, jewelry). Lengths of fingers were calculated from these images using the measuring toolbar of Adobe Acrobat (accurate to 0.01mm). Digit length was defined as distance from the crease in the skin nearest the palm, to the tip of the digit as is common protocol (Manning, Scutt, Wilson & Lewis-Jones, 1998). 2D:4D ratios were defined as 2nd digit length divided by 4th digit length (see Appendix, Figure D).

Previous research has found ethnicity to have a significant effect on 2D:4D ratios (Manning, Stewart, Bundred & Trivers, 2004; Manning, Churchill & Peters, 2007; Manning, Fink & Trivers, 2014) likely due to variation in allele distribution of the androgen receptor gene (Ackerman et al., 2011). In an effort to control for this the nationality of participants was recorded and from these, broader regional groups were formed (Norther, Europe, Eastern Europe, Asia etc; Appendix Figure B).

Go/NoGo task. This task was created and ran on E-Prime 2.0. Participants sat in a darkened room before a computer screen and were required to respond with their left and right thumbs on a response box. The task took 25-30 minutes.

This task featured green (Go) and blue (NoGo) arrows pointing left or right on a grey screen for a duration of 100ms. The Go:NoGo ratio was 3:1. Participants were required to press the left or right key in accordance with the arrow direction when they saw the Go but not the NoGo stimulus.

Responses were recorded if they occurred within 1000ms of the stimulus-onset. A fixation cross was present for between 2000 and 2500ms (jittered) before, and 900ms after, stimulus presentation (ITI = 3000 - 3500ms jittered). Training consisted of 20 trials, in which participants received trial-feedback. Testing consisted of 800 trials with breaks between every 80 in which participants received block-feedback (accuracy and RT). Participants were instructed to be both as fast and as accurate as possible.

EEG.

EEG acquisition. EEG was acquired during the task using 64 non-active, sintered Ag/AgCl electrodes arranged in a standard 10-10 configuration (Chatrian et al., 1985) and mounted on a flexible lycra cap. The tip of the nose served as the reference site, AFz as the ground, and two electrodes at the outer canthi of each eye recorded ocular movements. Electrodes were also attached to the participant's hands as part of another study. The signal was amplified by a Neuroscan EEG amplifier and recorded on Curry (Neuroimaging Suite 7) software. The sampling rate was 2500Hz was and a high-pass filter of .01Hz was applied online. During preparation of the scalp, impedances were kept below 5kΩ.

EEG preprocessing. EEG data were preprocessed and analyzed offline using the MATLAB toolbox, EEGLAB. Preprocessing of the signal involved the following steps:

Numerical stimulus and response triggers were recoded according to stimulus type (Go/ NoGo) and response outcome (correct/incorrect). Correct Go trials were defined as Go trials which were responded to with the appropriate response (left/right) within 1000ms of stimulus onset. Correct NoGo trials were defined as those for which no response was detected between stimulus onset and 1000ms post-stimulus onset.

The signal was filtered with a 35Hz low-pass filter, resampled to 350 samples per second and epoched into 1 second segments. Epochs were time-locked to Go or NoGo stimuli with a 200ms pre-stimulus baseline and a 800ms post-stimulus period.

An independent components analysis (ICA) was performed and ocular and muscular artifacts were identified by visual inspection of these components. The number of components removed ($M = 7.35$, $SD = 3.34$) did not differ across gender. An automatic trial rejection procedure rejected epochs of the decomposed data if they contained component amplitudes greater than ± 14 *SD*s of any component's mean (eeglab function: pop_eegthresh). This required that activity for each component be normalized before thresholding. A second criterion rejected epochs if observed component activity exceeded probabilistic values for that component (local threshold) or for the whole dataset (global threshold) by more than ± 8 *SD*s (eeglab function: pop_jointprob). The number of epochs rejected ($M = 37.38$, $SD = 27.50$) did not differ by sex and equivalent proportions of Go and NoGo epochs were rejected.

The data was then back-projected to EEG channel data. One participant required interpolation of data for one channel (CP2) which was performed using the spherical method. Finally, correct Go and correct NoGo epochs were averaged.

N2.

N2 peak amplitude. Three electrodes of interest were chosen as the most likely to exhibit an N2 effect based on the frontocentral topography of the N2. N2-peak was defined as the global minima between 190 and 330ms post-stimulus. Quality checks ensured the peak within this window was correctly identified for all subjects. We used the difference in peak N2 amplitudes instead of the peak of the difference ERP as the N2 index of interest given peak latency differences across

conditions.

N2 mean amplitude. Mean amplitude was the mean potential between 220 and 250ms post-stimulus. This window was based on the average peak latency for the grand-averaged NoGo ERP across three frontal electrodes (Fz, FCz and Cz) ±15ms.

MRI.

MRI acquisition. Images were obtained on a 3T MRI scanner (Siemens Skyra) using a T1-weighted spoiled gradient echo-pulse sequence with the following parameters: TR = 4.66ms, TE = 2.32 ms, 8º flip angle, matrix size = 256 x 256 x 184 mm, voxel size = $1mm^3$.

MRI preprocessing & asymmetry classification. All preprocessing of MR images was done using CAT12 (Computational Anatomy Toolbox; Gaser & Dahnke, 2016) an extension to SPM12 that allows for surface-based morphometric measurements.

T1 images were normalised to a template space and segmented. SPM12 tissue probability maps were used for the initial spatial registration and segmentation. The left and right central cortical surfaces were reconstructed using a projection-based thickness method. The gyrification index was found by estimating the "smoothed absolute mean curvature" across the central cortical surface. Curvature values from each vertex of a spherical surface mesh are first averaged within 3mm areas. This small region adopts the absolute value of this average. Finally, the absolute mean curvature values are smoothed using a surface-based heat kernel smoothing filter (Chung et al., 2005) of full width at half maximum (FWHM) of 25mm. This relatively large kernel was chosen on the basis that it optimally enhances features in the range of the distance between sulci and gyri, which is about 20-30mm. See Luders et al. (2006) for a more detailed description of this gyrification index.

The mean gyrification index (GI) within a region of interest (ROI) was calculated for an area corresponding to the dACC, but defined by the Desikan-Killiany atlas as caudal ACC (Figure 4; Desikan et al., 2006). Mean gyrification was calculated within this ROI for each hemisphere, and an index of asymmetry was created by dividing left dACC GI by right dACC GI. In this index, a score of 1 corresponds to symmetry and scores greater than 1 corresponded to leftward-biased asymmetries (M = 1.04, SD = 0.11, min = 0.85, max = 1.23).

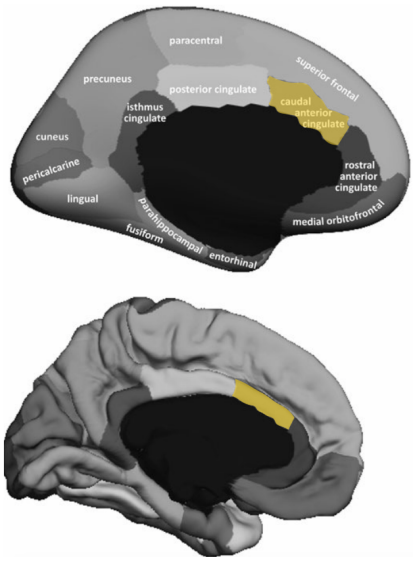

Figure 4. Region of interest marked in yellow, defined by the Desikan-Killiany atlas.The top image shows inflated surface with sulal fundi exposed. Images from Klein & Tourville (2012)

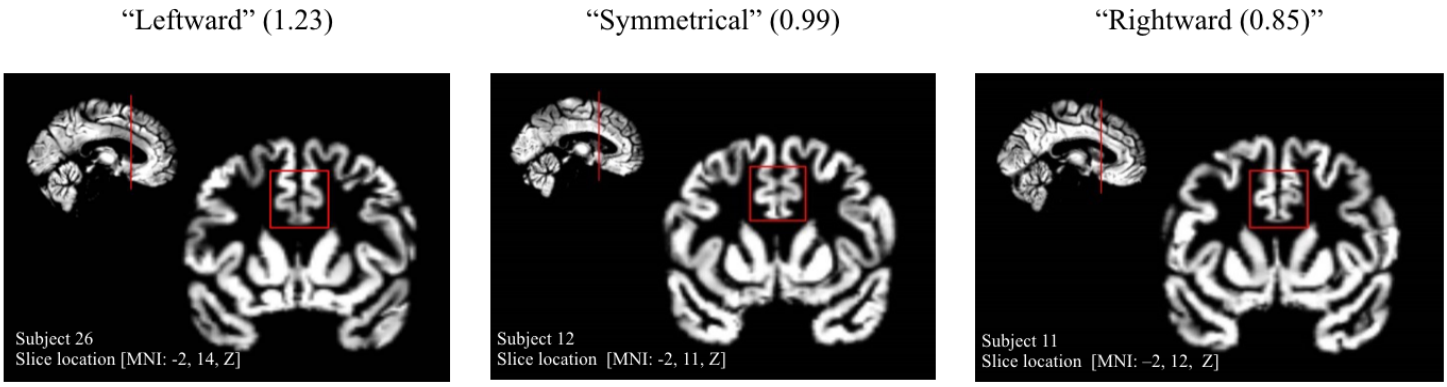

Figure 5. Coronal slices from the most extreme cases of asymmetry and a case of relative symmetry. Slice location marked with red line on sagittal view in top left. Red square indicates the general position of both CS and PCS. Slices taken from normalized grey matter volumes within the ROI.

Statistical Analyses

A repeated-measures ANOVA was performed to confirm the typical spatial configuration and conditional-dependency of the N2. Nine electrodes were chosen for this analysis (Fz, Cz, Pz, F3, F4, C3, C4, P3, P4) on the basis that they covered a wide area of scalp. Mean amplitudes with a 30ms window were used for this analysis as posterior sites often do not have N2 peaks. The

dependent variable was mean amplitude and factors included were task condition (Go, NoGo), scalp longitude (frontal, central, parietal) and latitude (left, middle, right).

An independent samples t-test was used to test sex differences in ACC gyrification asymmetry (H1). Pearson's correlations tested the hypothesised relationship between gyrification asymmetry and the 2D:4D finger ratios (H2), as well as the relationship between gyrification asymmetry and the conditional differentiation of N2 (H3). A mixed ANOVA was used to explore sex differences in the conditional N2 difference across three frontal electrodes (H4). An ANCOVA was used to check if this effect was altered by covarying for gyrification asymmetry. Bonferonni corrections were used for all post-hoc tests of AN(C)OVA effects. Greenhouse–Geisser epsilon corrections were used when the assumption of sphericity was violated.

We chose to test H3 using a 1-sided test given that all evidence for the effect to date has been in one direction (leftward asymmetry of ACC gyrification and greater conflict-related N2 amplitudes). Two-sided tests were chosen for all other hypotheses.

Finally, given the small sample size we also estimated the reliability of point estimates with bootstrapped confidence intervals (1000 iterations).

Statistical tests were carried out in IBM SPSS Statistics 24. Bootstrapped tests were performed in MATLAB when not available in SPSS.

Results

Behavior

Go and NoGo accuracies were positively skewed while reaction times showed a relatively normal distribution. The medians and variances of these behavioral variables, split by gender, are displayed in Table 1. Independent-samples median and Mann-Whitney tests indicated that there were no significant gender differences in the median or distribution of Go or NoGo accuracies. An

independent samples t-test showed there was no significant sex difference in Go RTs.

Table 1. *Behavioral Results on the Go/NoGo Task by Gender*

	Variable	Median	(25th & 75th percentile)
Females (*n* = 19)	Go Accuracy (%)	95.67	(94.00, 97.00)
	NoGo Accuracy (%)	99.50	(99.00, 100.00)
	Go RT (ms)	400	(384, 422)
Males (*n* = 17)	Go Accuracy (%)	96.17	(92.08, 97.42)
	NoGo Accuracy (%)	99.50	(98.50, 100.00)
	Go RT (%)	400	(373, 436)
Total (n = 36)	Go Accuracy (%)	95.92	(93.58, 97,00)
	NoGo Accuracy (%)	99.50	(98.63, 100.00)
	Go RT (%)	400	(376.63, 422.93)

Conditional and Spatial Specificity of The N2

There was a strong main effect of condition on the N2 ($F_{(1,35)} = 22.04$, $p < .001$, $\eta_p^2 = .39$) such that NoGo amplitudes were more negative than Go amplitudes ($M_{Diff} = -0.41$, $p < .001$). The two spatial parameters longitude and latitude, showed interaction effects with condition on mean negativity. Amplitudes across the longitudinal axis of the scalp differed as a function of condition ($F_{(1.43, 49.90)} = 11.74$, $p < .001$, $\eta_p^2 = .25$) such that the conditional difference in amplitudes (NoGo - Go) was only significant at frontal sites ($M_{Diff} = -1.02$, $p < .001$). Regarding the interaction between latitude and condition ($F_{(1.69, 59.27)} = 12.56$, $p < .001$, $\eta_p^2 = .26$)— the conditional difference was significant at both midline ($M_{Diff} = -0.66$, $p < .001$) and right hemisphere sites ($M_{Diff} = -0.45$, $p < .001$). Finally there was a 3-way interaction of condition, longitude and latitude ($F_{(2.81, 98.35)} = 4.21$, $p = .009$, $\eta_p^2 = .11$) driven by significant conditional differences at all frontal electrodes (F3, Fz, F4;

all $p < .001$) and the central-midline (Cz; $p = .005$). These results support that the N2 is amplified in the low-probability relative to high-probability condition and that this effect is maximal at frontocentral sites (Folstein & van Petten, 2008).

Hypothesis 1

Females had a more leftward asymmetry index ($M = 1.06$, $SD = 0.11$; $n = 20$) than males ($M = 1.00$, $SD = 0.09$; $n = 15$) however this difference was not significant ($t_{(33)} = 1.60$, $p = .12$, 95% CI [-0.01, 0.12]). Figure 6 illustrates the hemispheric contribution to these asymmetry scores. Only 35% of bootstrap simulations showed a significant sex difference in gyrification asymmetry.

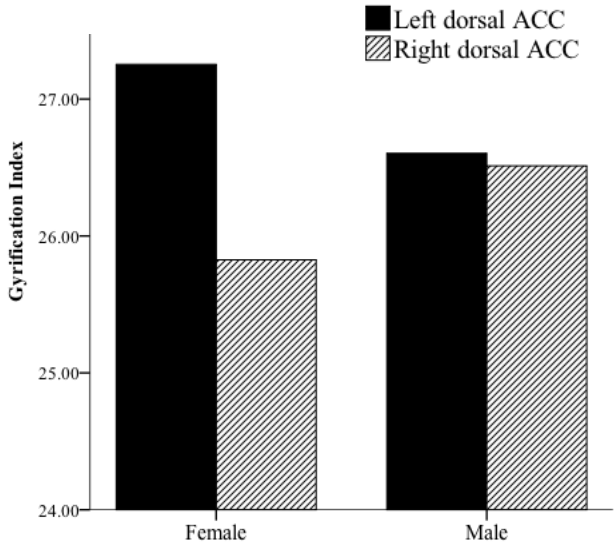

Figure 6. Gyrification indices within each hemispheric ROI (dorsal ACC) across males and females. Females show greater asymmetry in gyrification within this region than males.

Hypothesis 2

Across the entire sample, there was no correlation between gyrification asymmetry and 2D:4D, neither in the left hand 2D:4D ($r = -.02$, $p = .90$) nor right-hand 2D:4D ($r = -.01$, $p = .93$).

Distribution across putative ethnic groups was too sparse to include this variable as a covariate (Appendix, Figure B). Further, it did not seem reasonable to merge groups again given previous findings suggest differences in the 2D:4D even at the intra-continental level (Manning et al., 2014; Voracek & Dressler, 2006). Thus we decided to test this hypothesis in the largest ethnically homogenous group available: Northern Europeans ($n = 14$, 7 males).

Correlations between gyrification asymmetry and 2D:4D ratio were much larger in this

subsample than the whole (Table 2) despite a lack of a sex difference in ACC gyrification asymmetry in this subgroup. The direction of associations in this subsample indicated that the lower the 2D:4D finger ratio, the more leftward asymmetry was observed in dACC gyrification.

Table 2. *Correlations Between 2D:4D Finger Ratios and ACC Gyrification Indices (GI) for Northern Europeans (n = 15) and Reliability Estimates [Bootstrapped 95% Confidence Intervals]*

	Left Hemisphere GI	Right Hemisphere GI	Gyrification Asymmetry (L > R)
Left 2D:4D	-.56 [-.86, .18]	-.36 [-.83, .10]	-.42 [-.80, .34]
Right 2D:4D	-.47 [-.82, .12]	-.11 [-.69, .49]	-.45 [-.80, .06]

Additional exploratory analyses on gyrification within each hemisphere indicated that this was driven by associations between 2D:4D finger ratios and *left* ACC gyrification rather than right-ACC gyrification. However, wide 95% confidence intervals around zero indicated the low reliability of most of these correlations.

Hypothesis 3

There were trend correlations between gyrification asymmetry and the conditional difference in N2 amplitudes at Fz (r = -.28, p = .06, 95% CI [-.60, .08]) and FCz (r = -.25, p = .08, 95% CI [-.54, .05]) in the expected direction (leftward asymmetry related to greater negativity).

To illustrate how the N2 conditional effect varied across the asymmetry index, the index was split into three equal segments with

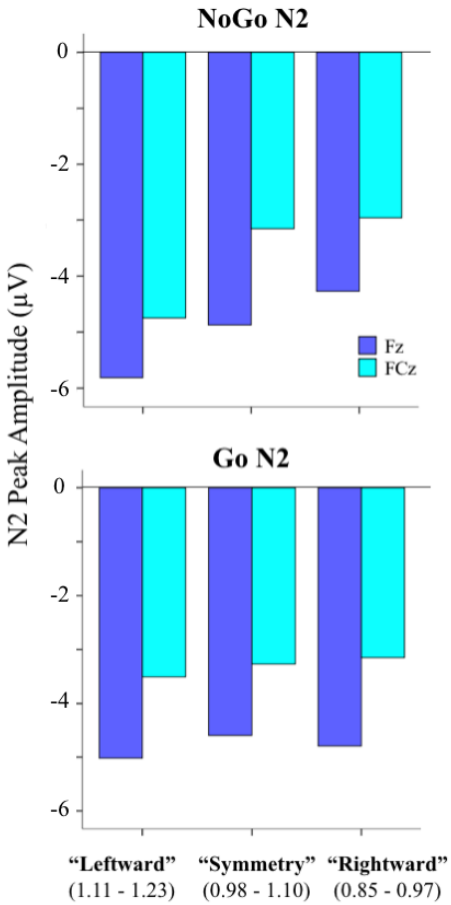

Figure 7. NoGo-N2 amplitudes show greater group differences than Go-N2 amplitudes

sample min and max at the extreme ends (0.85 - 0.97; 0.98 - 1.10; 1.11 - 1.23). Figure 7 indicates that the relationship between the asymmetry index and the magnitude of conditional differentiation of N2 amplitudes was due to relative amplification of the *NoGo-N2* among those with more leftward asymmetrical folding patterns. NoGo-related topographies and ERPs were averaged across participants falling in each third (Figure 8). Note these groups are only used to demonstrate incremental differences in ERPs and topologies and were not statistically analysed.

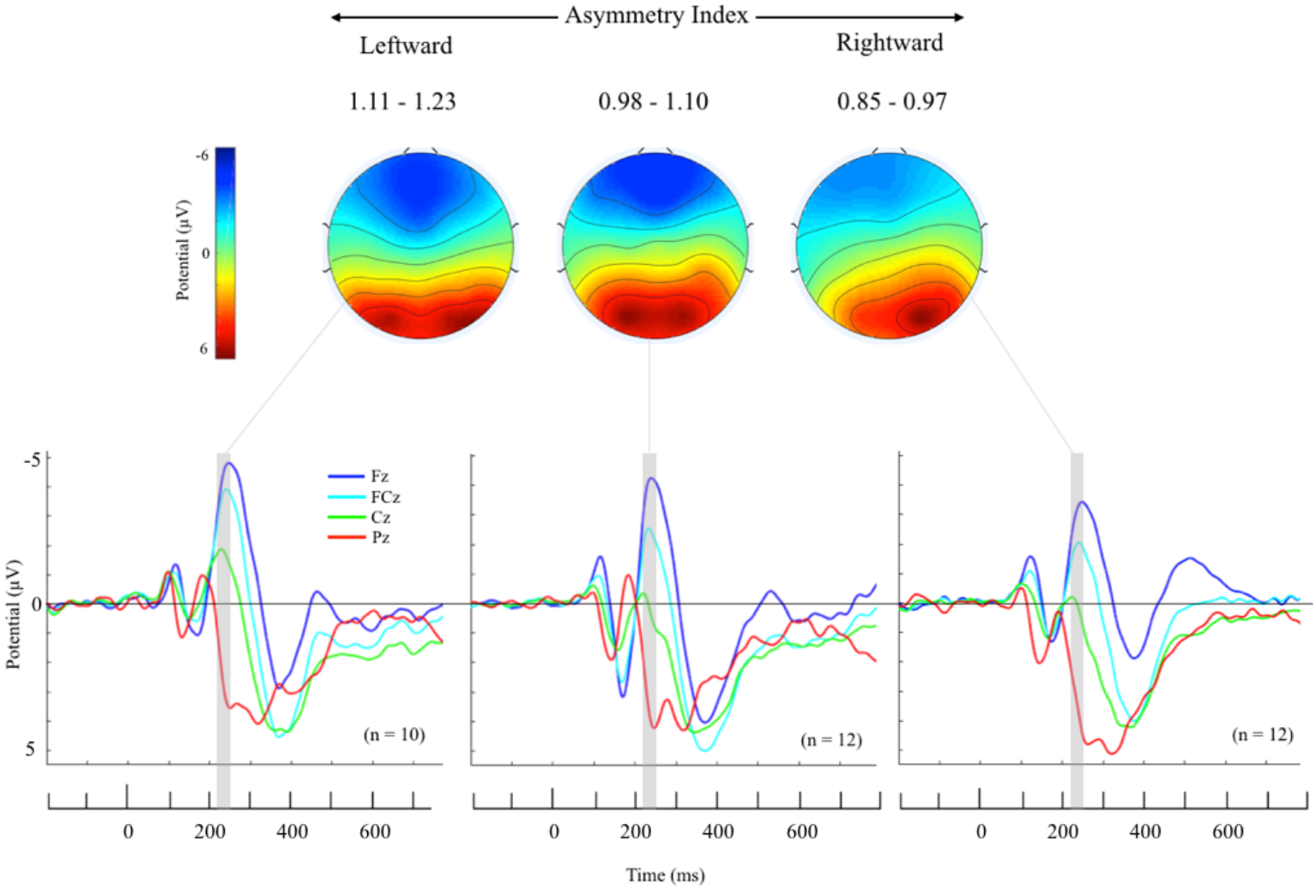

Figure 8. (Top) NoGo topographies averaged across the time window marked in grey (220-250ms); (Bottom) NoGo ERPs across 4 midline electrodes for 3 ranges on the ACC gyrification asymmetry index. Note larger frontocentral N2 peak amplitudes (blue, cyan, green) in those with leftward asymmetries.

Hypothesis 4

To test whether there were sex differences in the conditional N2 effect, a mixed ANOVA was performed on conditional differentiation of N2 amplitudes. Electrode (Fz, FCz, Cz) was also included as the within-subjects factor.

We found a main effect of sex on the conditional N2 effect ($F_{(1,34)} = 6.84$, $p = .01$, $\eta_p^2 = 0.17$). Observation of means (Table 3) and ERPs (Figure 9) suggests this effect is driven by greater differentiation of NoGo and Go-N2 amplitudes in females compared to males. This main effect of sex on N2 could be replicated in 75% of bootstrap samples. Paired samples t-tests within each sex showed that the conditional difference in N2 amplitudes was significant only for females, at FCz ($t_{(18)} = 2.17$, $p = .04$) and Cz ($t_{(18)} = 2.51$, $p = .02$). The interaction effect of sex and electrode was not significant.

Given that ACC gyrification asymmetry covaried with the dependent variable (H3), we included this as a covariate in the model. Homogeneity of covariate regression coefficients was observed in sex-split scatterplots of the covariate and the dependent variable. The effect of sex became non-significant after including this covariate ($F_{(1,31)} = 3.90$, $p = .06$, $\eta_p^2 = .11$). No main or interaction effect of electrode was found, nor was there a main effect of ACC gyrification asymmetry. Means and standard deviations of N2 amplitudes across sex, condition and electrode are displayed below.

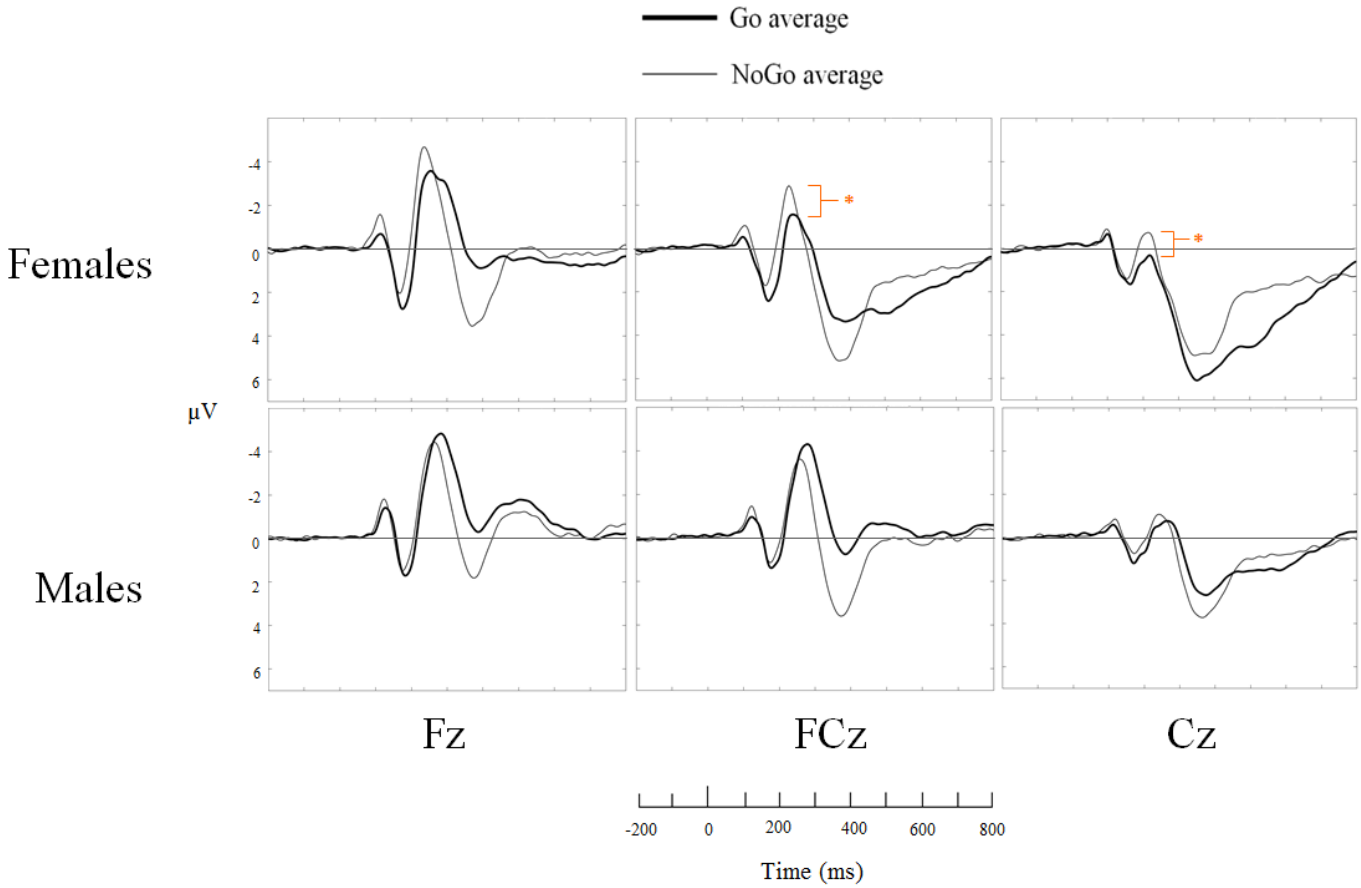

Figure 9. Go and NoGo ERPs at Fz, FCz, Cz for males and females. *$p < .05$

Table 3. *Means (and Standard Deviations) for Go- and NoGo-N2 Peak Amplitudes in Males and Females across Three Frontal Electrodes*

		N2 amplitude			
		Go		**NoGo**	
Males (n = 17)	**Fz**	-5.35 (1.93)		-5.04 (1.74)	
	FCz	-4.78 (2.27)	-3.88 (1.77)	-4.22 (2.08)	-3.62 (1.68)
	Cz	-1.51 (2.13)		-1.59 (1.66)	
Females (n =19)	**Fz**	-4.16 (4.13)		-4.64 (4.27)	
	FCz	-2.10 (3.57)	-1.89 (3.23)	-2.86 (3.83)	-2.85 (3.38)
	Cz	0.60 (3.71)		-1.04 (2.35)	

Discussion

In summary, we first found a trend sex difference in gyrification asymmetry in the opposite direction to what had been previously found. As will be discussed, the cortical atlas used to define the dACC may account for this difference. Second, we found that lower more "male-typical" 2D: 4D ratios were related to more leftward asymmetries, however this was a weak correlation and was only found in a ethnically homogenous subsample. Third, we found that a leftward asymmetrical gyrification pattern in ACC was related to greater conditional differentiation of N2 amplitudes in keeping with previous findings (Huster et al., 2009, 2014). Finally, sex differences were observed in this conditional differentiation of the N2, a difference partially accounted for by asymmetrical gyrification of the dACC. Results are discussed in greater detail below.

Sex differences in ACC gyrification (H1)

On average, while males exhibited relative symmetry, females exhibited a slightly leftward asymmetrical gyrification. Albeit a non-significant difference, this is in conflict with the findings of Yücel et al. (2001; Figure 2) and Huster et al. (2007) who both found leftward asymmetries to be more common in men, and symmetry to be more common in women. This contradiction may be explained by the following…

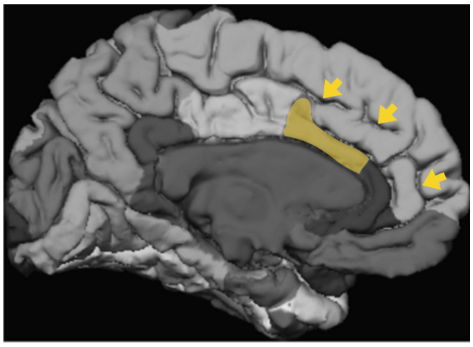

Figure 10. Yellow arrows indicate PCS segments which were not included in the ROI (shaded yellow)

One of the limitations of the regional parcellation procedure used in this study was that the PCS, when present, was not included in the definition of the ROI, and thus was excluded from

gyrification calculations (Figure 10)[1]. That is, asymmetry found by this method more likely reflect asymmetry of the CS, other minor sulci radiating from the CS or the callosal sulcus.

This said, the compensatory relationship between neighbouring sulci (Connolly, 1940) means that variation in CS and other tertiary sulci are likely influenced by PCS presence and prominence, albeit indirectly. To visualise what the ROI-averaged gyrification index reflects, left medial surfaces for those with highest and lowest GI values are displayed in the Appendix (Figure A). These show that hemispheres with the highest GIs have narrower cingulate gyri, consistent with the effect of PCS presence (Vogt et al., 1995; Leonard et al., 2009; Figure 1). Additionally, those with higher GIs appear to show more PCS segments (as defined as any segment running parallel and dorsal to the CS; Yücel et al., 2001) though as already mentioned, our gyrification method could not capture the metrics of this sulcus directly. There are two possible methodological explanations for this. First our GI is based on the *curvature* at every point of cortex. Relatively flat regions on gyral peaks are considered to have low GI due to their near-zero curvature. The tendency for the cingulate gyrus to have a larger surface area when the PCS is absent (Vogt et al., 1995), and the low curvature values across gyral peaks may explain why low mean gyrification within the ROI may indicate PCS presence. Alternatively, PCS presence may be reflected in the GI as a function of sulcal frequency: our GI takes into account the frequency of cortical folds as well as their depth, thus a sulcal doubling of the ACC may result in a higher GI within the ROI, even if the ROI does not contain both sulci, as a result of smoothing.

Thus we can say that females showed greater asymmetry in gyrification within the dACC, and this may have been influenced by PCS prominence, indirectly, or by other sulci, the functional significance of which are not yet understood.

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[1] An adapted version of our cortical parcellation scheme is available (Klein & Tourville, 2012), which corrects for this failure to include paracingulate regions in the ROI. However this version was not available in CAT12's surface morphometry toolbox at the time of analysis.

Prenatal Hormones: a plausible influence on ACC gyrification asymmetry? (H2)

We did not find a correlation between 2D:4D of either hand and gyrification asymmetry in the full sample however it is likely that ethnic heterogeneity posed a major source of noise to 2D: 4D correlations.

Within the largest group available, Northern Europeans (n = 14), medium-sized correlations were found between the 2D:4D and the extent of asymmetry such that lower "male-typical" finger ratios were associated with a more leftward asymmetry. It is interesting to note that this correlation existed in absence of a sex difference in gyrification asymmetry in this subsample. This is tentative support for the use of 2D:4D as a more sensitive marker of sex hormone-linked brain variation than the sex dichotomy.

We do not want to weigh too much on this finding given the statistical unreliability of this effect and the specific group to which it refers. However stronger correlations between 2D:4D ratios and hemispheric gyrification in the left, rather than in the right, suggests that the previously found greater variability in left ACC sulcal patterns might be explained by the same prenatal hormone variation which influences the 2D:4D finger ratio. Huster et al. (2007) found that discrepancies in PCS asymmetry across sex and handedness stemmed from variations of cingulate morphology in the left hemisphere, and Yücel et al. (2002) found that schizophrenics differed from controls in the extent of left but not right ACC gyrification. Geschwind and Galaburda (1987) argue that it may be the earlier and more prolonged maturation of the left cerebral hemisphere that renders it more susceptible to circulating steroid hormones and that this may account for males greater likelihood of becoming right-brain dominant (and left-handed).

The only other study that has directly investigated links between ACC morphology and the 2D:4D finger ratio, found a positive correlation between grey matter volume in the dACC and 2D: 4D ratios, after controlling for gender and age (Gorka, Norman, Radtke, Carré & Hariri, 2015).

Lower "male-typical" 2D:4D ratios were associated with *reduced* left dACC volumes. Given that this cluster appears to be situated on a gyral peak (Appendix, Figure C) and given that sulcal prominence and adjacent gyral expansion are inversely related (Vogt et al., 1995; Figure 1D), these findings are consistent with our finding of low 2D:4D ratios and *greater* gyrification of the left dACC.

Structure-Function links in the ACC (H3)

The direction of our structure-function hypothesis was confirmed: leftward asymmetry of ACC gyrification was related to greater conditional differentiation of N2 amplitudes. The convergence of this result with past research (Huster et al., 2009, 2014) is interesting given methodological differences. Notably, Huster et al. focused exclusively on PCS length while our approach took the curvature of the surface within the ROI which, as discussed above, could only have included PCS-related variation indirectly.

Could it be that the functional significance of an asymmetric gyrification pattern is rooted in the asymmetric prominence of the PCS, and that our method captured some downstream effects of this, plus some other curvature-related "noise"? In support of this, the occurrence of a PCS has been linked to a relative expansion of cytoarchitectural area 32' and its occupation of the gyral peak rather than the sulcal fundus or wall (Vogt et al., 1995; see Figure 1D). While there has been no direct microstructural investigation of the cognitive effects of expansion of this cytoarchitectural area— its greater size in humans, particularly in the left hemisphere, relative to primates (Paus et al., 1995; Paus, 2001) and recruitment of left paracingulate gyrus during task tapping executive functions such as spatial working memory and planning (Fornito et al., 2004; Dagher et al., 1999; Duncan & Owen, 2000) has been interpreted as evidence for the functional significance of PCS asymmetry.

One could argue that variation in N2 amplitude across this structural asymmetry index simply reflects differences in dipole orientation, a plausible theory given PCS-dependant movement of cytoarchitectural areas from sulcal fundus to gyral peak (illustrated in Figure 1). Source analyses were not carried out in this study, however Huster et al. (2014), investigating the same structure-function relationship, used performed a dipole source analysis to assess whether scalp-recorded ERP differences across subjects were attributable to differences in dipole location or orientation. They seeded an equivalent-current dipole to a midcingulate region (Talairach coordinates [x, y, z]: 0, 2, 33) with its orientation free to rotate, and found that differences in scalp-recorded N2 amplitudes between those with leftward-biased PCS patterns and other types of PCS patterns, did indeed stem from differential engagement of the fixed midcingulate source. The authors argue that if ERP differences reflected topographical differences due to variation in gyral orientation, no differences between the structurally-relevant groups would be observed at the source level using fixed dipole location and data-driven orientation.

Dampened frontocentral negativity does not necessary imply "worse" processing of NoGo stimuli. Indeed this is supported by the lack of correlation between the gyrification asymmetry index and any behavioral outcome. Similarly, other studies have failed to find a dependency of successful inhibition rates on N2 amplitude (Kok, Ramautar, de Ruiter, Band & Ridderinkhof, 2004; de Jong et al., 1990; Pliszka, Liotti & Woldorff, 2000). The fact that those exhibiting rightward asymmetries showed greater P3 amplitudes than the leftward asymmetry group (inferred from Pz amplitudes at 300ms; Figure 8) may reflect differential emphasis on the processes underlying each component. Huster et al. (2009) found a similar phenomenon in Stroop-related ERPs: subjects with a symmetrical absence of PCS showed a diminished N400 but a more pronounced positivity over posterior electrodes in a subsequent time-window, compared with subjects with a leftward PCS asymmetry. The authors inferred that the left asymmetrical-PCS group

relied more on early conflict monitoring processes, while the symmetrically PCS-absent group relied more on later, effortful attentional control processes. Our results suggest that a similar frontocentral-negativity vs parietal-positivity strategic trade-off exists in the Go/NoGo task and is influenced by ACC morphology.

Sex differences in N2 amplitudes (H4)

The finding of greater conditional differentiation of N2 amplitudes among females is consistent with Yuan et al. (2008) who showed greater N2 differentiation in females to deviant vs standard stimuli in an oddball task. Like our Go/NoGo task, the oddball task involves a frequent and infrequent response but unlike the Go/NoGo, it lacks an element of inhibitory control. Inferring from the common demands of both tasks, it may be that females have a relatively larger N2 response to such violations of expectations rather than to response demands per se, though further research will need to elucidate whether the presence of a sex difference in the N2 is dependent on the probability or inhibitory demands of the stimulus.

There are however studies showing the opposite sex difference. Omura and Kusumoto (2015) analysed N2 amplitudes across two conditions: a cued response (O followed by X) and cued inhibition (O followed by any other letter) which both had equal probabilities. Males showed higher N2 amplitudes regardless of condition and no sex X condition interactions was present. We argue that absolute amplitudes are a worse metric for investigating individual differences in functional electrophysiology than the relative amplitude differences across conditions given the contribution of bone and tissue factors to the EEG signal (Nunez & Srinivasan, 2006). Indeed males had overall more negative N2 amplitudes in our sample too, but this could plausibly be due to sex differences in total brain volume (Lange, Giedd, Castellanos, Vaituzis & Rapoport, 1997) or skull thickness (Pfefferbaum & Rosenbloom, 1987; Dijk, Beersma & Bloem, 1989).

Sex differences in N2 amplitudes, and not in any behavioral index of performance, suggests males and females can achieve equivalent inhibitory control with differential emphasis on this frontocentral negative component. Support for differential use of neural strategies across the sexes comes from ERP (Huster, Westerhausen & Herrmann, 2011) and fMRI studies (Li et al., 2006, 2009) which also show different patterns of regional activation despite equivalent inhibitory performance. Of note, Liu et al. (2012) and Li et al. (2006, 2009) have shown greater activation of ACC in males relative to females in successful (vs. unsuccessful) inhibition. This supports our findings given recently discovered links between *larger* inhibition-related N2 amplitudes and *de*activation of the midcingulate area (Baumeister et al., 2015).

Finally, the significance of this sex difference, in the traditional statistical sense, was dependent on ACC gyrification patterns, being reduced to a sub-alpha level after inclusion of this structural covariate. This suggests sex differences in conflict- and novelty-processing are at least partly mediated by brain structure, and more interestingly a structural factor which is established predominantly before birth (Zilles et al., 1997; Armstrong et al., 1995).

Limitations & Future Directions

The main limitation of this study was its failure to control or covary for ethnicity, given the centrality of the 2D:4D to our overarching theory of sex differences in the brain. Our sample was ethnically heterogenous and this likely contributed to the lack of a significant gender difference which is highly reproducible (Hönekopp & Watson, 2010) and, we speculate, to the lack of a relationship with gyrification asymmetry. It is difficult to interpret anything from our subsample analysis given the unreliability of correlations— these hypotheses must be tested in a more homogenous group in future, using either the 2D:4D finger ratio or direct amniotic samples to estimate prenatal hormone levels.

Another limitation of this study is its inability to delineate the contribution of specific sulci to the asymmetry index, and subsequently their relevance to N2 modulations. Previous studies have had the same problem but due to the exclusive focus on PCS asymmetry. It would be interesting to know whether it is indeed the leftward asymmetry of PCS or the concurrent reduction in the surface area of the cingulate gyrus (Paus et al., 1995) that is functionally relevant to electrophysiological markers and advantage on executive tasks. Future research should also consider using microstructural markers to elucidate the functional effects of large-scale movements of cytoarchitecturally distinct regions from sulcal depth to gyral peak.

Finally, Go-N2 amplitudes were unusually large in this study, particularly in males. It is possible that given speed demands of the task, the two-choice decision on Go trials was perceived as a response conflict, leading to a "conflict-related Go-N2". Alternatively, the Go-N2 may reflect residual motor potential, which tends to consist of a short negativity before responses (Kornhuber & Deecke, 1965; Shibasaki et al., 1980). However this seems unlikely as the motor potential is usually attenuated by the variance in RTs. Also it seems unlikely to account for the greater Go-N2 in males given that males showed greater variance in RTs (*SD* = 38.20) than females (*SD* = 28.11). A final possibility, is that large Go-N2 amplitudes reflect a trait-like speed-accuracy trade-off. Perri et al. **(**2015) suggested that larger N2 amplitudes are related to a preference for speeded over accurate responses. Our data support this explanation, at least within male participants: exploratory correlations between Go-N2 amplitudes and response times showed that greater (more negative amplitudes) related to faster responding among males (Fz = .39, FCz = .43 Cz = .39) while correlations were weaker among females (Fz = .20, FCz = .09, Cz = -.26).

Conclusions

These results contribute to the wealth of evidence showing males and females process executive task demands differently at the neural level. It indicates that one area in which information processing differs between the sexes is in the detection of conflicts or surprise, as indicated by the N2, and suggests that sex-linked variance in ACC surface morphology may help explain this. Regarding the hypothesised prenatal origins of these ACC gyrification patterns, our findings align with previous research showing the differential sensitivity of the hemispheres to environmental factors. However our tests involving our putative marker of prenatal hormones were not well powered and require replication in larger, more homogenous, sample.

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Appendix

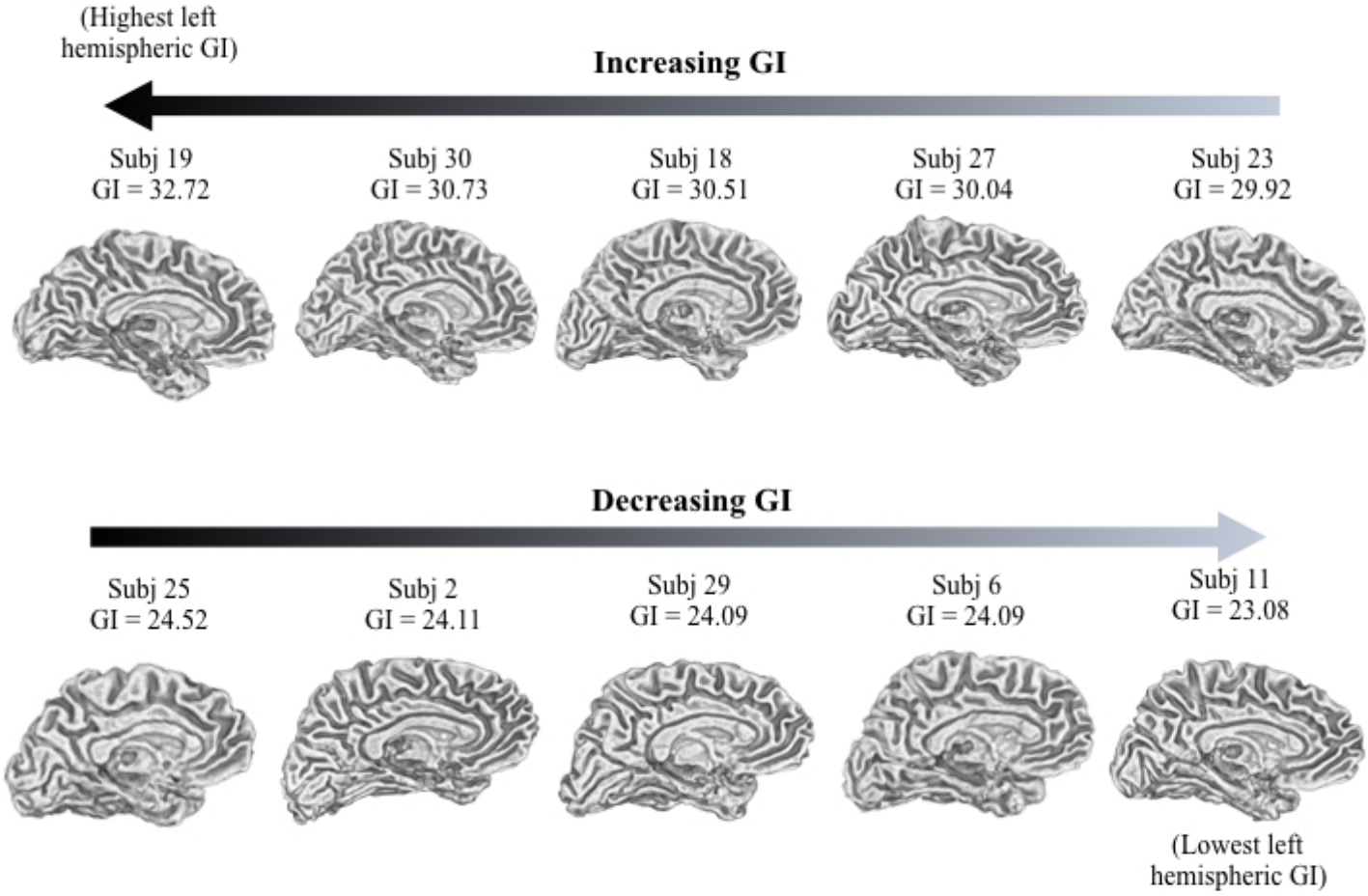

Figure A. Central surfaces for left hemispheres with the 5 highest (top) and 5 lowest (bottom) gyrification indices (GI). Noteworthy is the reduced cingulate gyrus surface area in its dorsal-ventral extent in those with high GIs compared to those with low GIs.

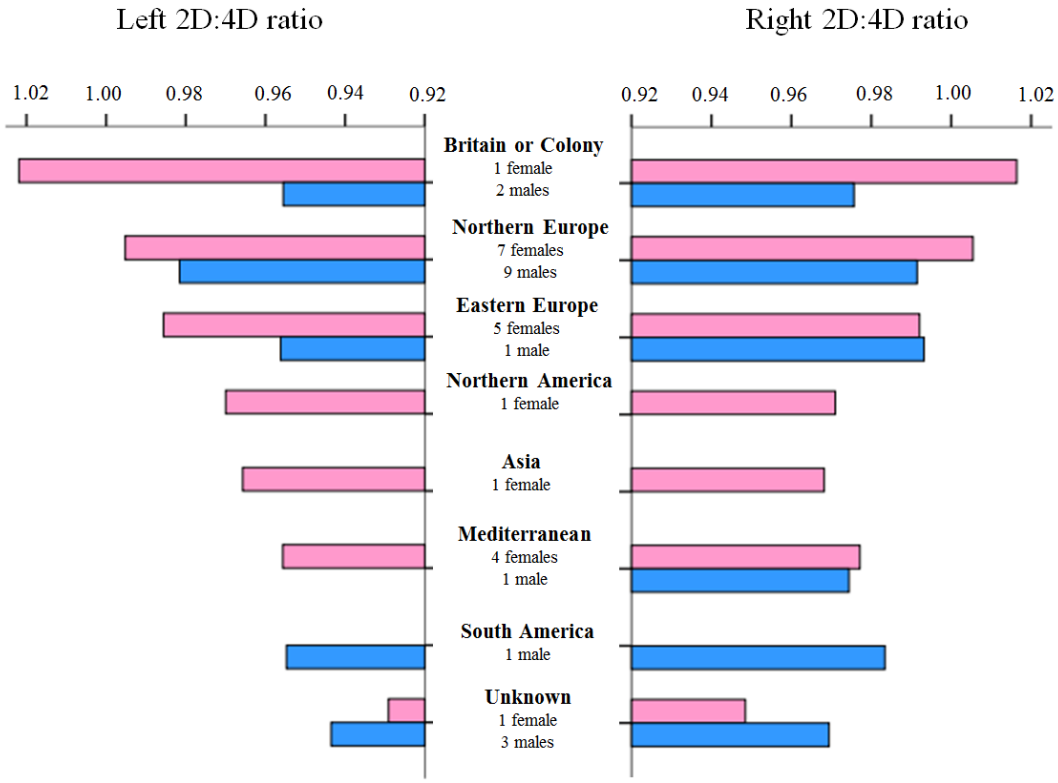

Figure B. Mean left and right 2D:4D finger ratios for males and females of each regional category in this sample. Regional categories were composed as follows: Britain and British colony (n = 3; Scotland, Australia), Northern Europe (n = 16; Norway, Sweden, Estonia, Germany), Eastern Europe (n = 6; Russia, Ukraine, Serbia, Czech Republic), Northern America (n = 1, Canada), Asia (n = 1, Thailand), the Mediterranean (n = 5; Spain, Italy, Portugal) and Southern America (n = 1; Mexico). Four participants did not provide their nationality. One male in the Mediterranean group had missing left 2D:4D data due to a hand deformity.

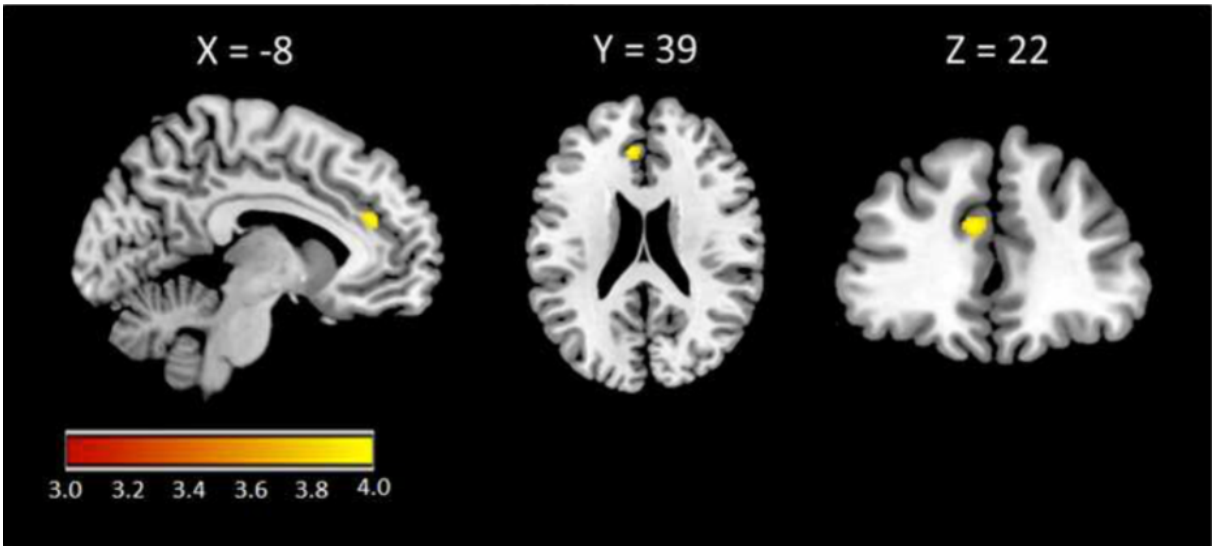

Figure C. Results of Gorka et al. (2015): Right hand 2D:4D ratio was positively correlated with gray matter volume within the left dorsal ACC (dACC) after controlling for age and gender ($N = 464$).

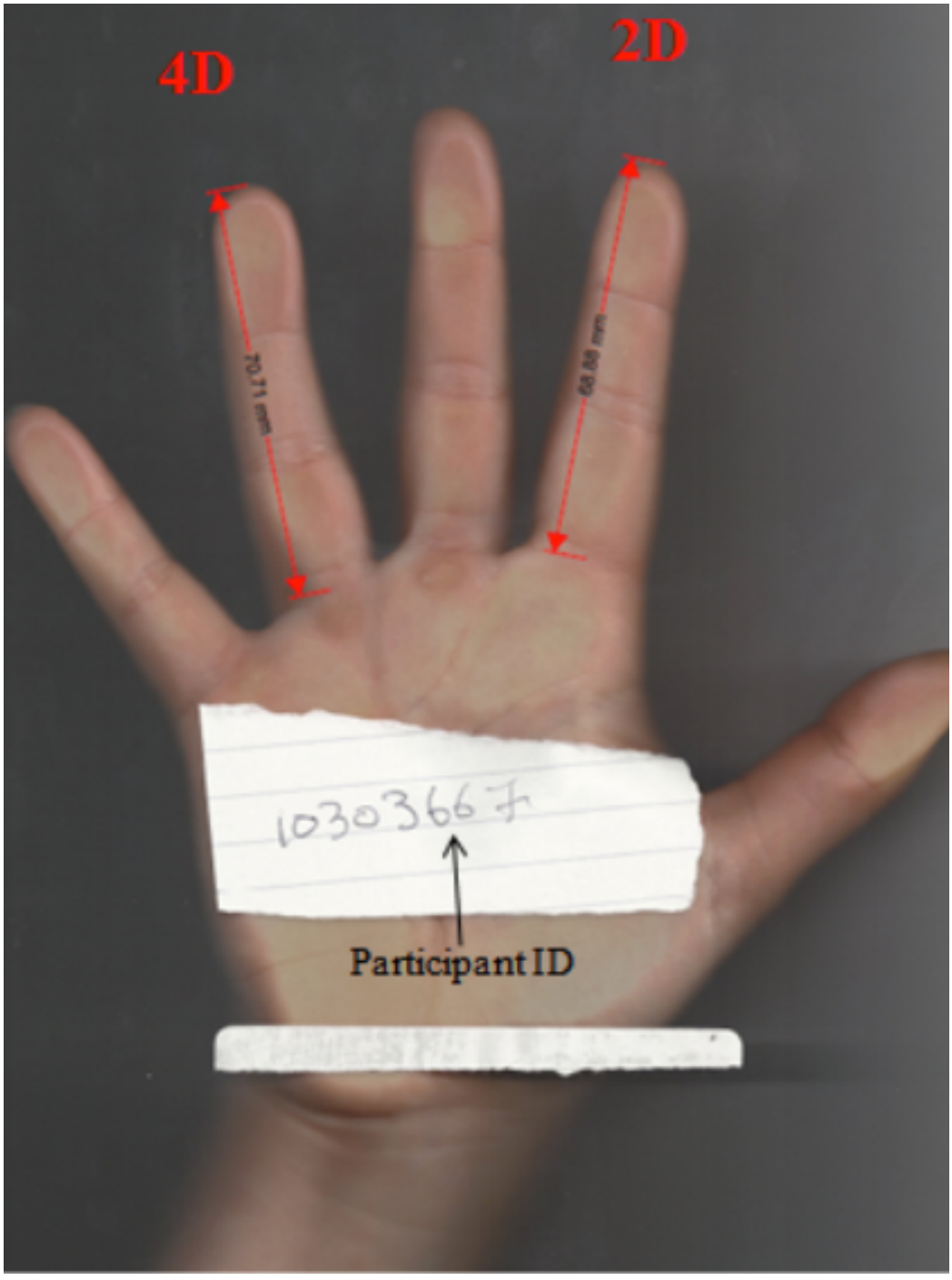

Figure D. Example of a hand scan with 2D and 4D lengths calculated using the Adobe Acrobat measuring toolbox.