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Title: Invisible cortex sign: a highly-accurate feature to localize the inferolateral central sulcus

Running Head: Central sulcus brain MRI DWI sequences

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Abstract

Introduction: The central sulcus is a key landmark on MRI of the brain, but its inferolateral portion is difficult to identify if unable to trace the sulcus superoinferiorly. The authors observed that the cortex abutting the central sulcus appears isointense to the adjacent white matter on DWI, we named this the "invisible cortex sign" and our study evaluates whether it could be used to identify the inferolateral central sulcus.

Methods: Observational study of 108 consecutive "normal" MRI studies performed from May 2016 to January 2017. A single axial DWI image – obtained in the anterior commissure-posterior commissure plane – was selected from each scan just above the subcentral gyrus such that it included the most inferolateral portion of the central sulcus. These single images were given to 10 readers (neuroradiologists, a neuroradiology fellow and radiology trainees) who marked the central sulcus based on the presence of the "invisible cortex sign". Their accuracy in identifying the central sulcus was compared with that of the principal investigators, who used tri-planar T1 volumetric MRI sequences.

Results: 108 consecutive patients (55 female, 53 male) were selected, ranging from 18 to 81 years old (mean=40.5, σ=18.2). The central sulcus was correctly identified in 95.5% of cases (σ=3.7%; range 89.4 to 99.1%).

Conclusions: The "invisible cortex sign" is a highly accurate method of identifying the inferolateral central sulcus on a single axial DWI slice without relying on the more superior aspects of the sulcus.

Keywords

Magnetic resonance imaging, brain, central sulcus, diffusion weighted imaging, neuroradiology.

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Text

Introduction

The central sulcus is a key landmark when interpreting neuroimaging as it allows for the localization of the primary motor cortex (anteriorly) and primary sensory cortex (posteriorly). As such, identifying the central sulcus with confidence is critical for surgical planning as well as correlating clinical symptoms with the location of pathology seen on imaging.

Many techniques and signs have been described to aid identification of the central sulcus on cross-sectional imaging. It can be argued that true localization of the primary motor cortex can only be definitively performed functionally, for example with BOLD fMRI, however, this is not available in most practices and even when available is not performed as part of routine imaging. These mostly rely on sulcal and gyral morphology and include the bracket sign, midline sulcus sign, L sign, T sign, thin postcentral gyrus sign, sigmoidal hook sign, bifid postcentral sulcus sign, M sign and U sign (1-4).

These landmarks are variably helpful in identifying in the central sulcus, and their reported anatomical presence varies between 54.5% and 98.9% (3). Importantly, however, the majority of these signs are focused on the superior most aspect of the central sulcus. The inferolateral portion of the central sulcus is more difficult to identify without the ability to trace the sulcus down from above, such as in situations where the more superior part of the brain is distorted or damaged by pathology. Described landmarks for adult brains rely on regional gyral morphology of the inferior frontal and subcentral gyrus (M and U signs respectively), and in both instances utilize sagittal imaging. Wagner et al. report the M-sign and U-sign to be anatomically present in 88.2% and 98.9% of patients respectively on magnetic resonance imaging (MRI). However, these studies did not assess how accurate radiologists were at identifying these signs (3).

Some studies have also noted differences in the T1 and fluid-attenuated inversion recovery (FLAIR) signal intensity of the cortex abutting the central sulcus and have also been described as being useful in localization(5-8).

We became aware that signal change is quite pronounced on diffusion weighted imaging, with the cortex abutting the central sulcus becoming isointense with the adjacent white matter – an appearance we have named the "invisible cortex sign" (Figure 1). The "invisible cortex sign" may be particularly helpful in cases where only diffusion weighted sequences are required, such as in localizing the site of an acute infarct, without needing to trace other surface anatomy to localize the site or correlating with another sequence/plane with the same finding. In this study, we sought to evaluate whether this feature in isolation could be

used to identify the inferolateral aspect of the central sulcus in adults without relying on the more superior anatomy.

Methods

Approval from our institutional ethics review board was obtained in accordance with National Health and Medical Research Council guidelines; consent from patients was waived given the negligible risk of the study. The local PACS was queried for consecutive MRI scan protocols "MRI Brain Epilepsy" and "MRI Brain Inflammation" obtained as part of routine patient care between May 2016 and January 2017. These protocols were chosen as they include both axial echo-planar diffusion weighted imaging (DWI) sequences and T1 magnetization-prepared rapid gradient-echo (MPRAGE) volumetric acquisitions reconstructed in three planes, and these indications have a high rate of "normal" as well as a wide range of patient age. All patients were scanned on 3T MRI.

Patients were included if they had undergone MR brain imaging reported as "normal" by a consultant radiologist. Acceptable incidental findings were: minor and age-appropriate chronic small vessel ischemia; perivascular spaces and arachnoid cysts that did not distort the perirolandic region; incidental aneurysms; low lying tonsils and pontine telangiectasias.

Patients were excluded if there was any pathology with potential to affect the intensity of the cortex on the DWI sequence. This included but was not limited to: multiple sclerosis; parenchymal mass lesions; intracranial haemorrhage; vasculitis; infarction; previous surgical resection. Any cases where DWI or volumetric T1 MPRAGE with sagittal, axial and coronal

images were not available, or significant motion or artefactual degradation existed, were also excluded.

No restrictions were placed on age to avoid selection bias, although there were fewer older patients in our study population given they had a higher incidence of abnormal findings and were less likely to be scanned for the indication of "MRI Brain Epilepsy" and "MRI Brain Inflammation". Overall, 108 consecutive patients (55 female, 53 male) were selected (216 central sulci), ranging from 18 to 81 years old (mean=40.5, σ=18.2). Ages ranged from 19 to 78 for females (mean=39.1, σ=18.8), and 18 to 81 for males (mean=41.9, σ=18.1).

Each scan was de-identified and uploaded to the local picture archiving and communication system (PACS) research server (Synapse version 4.4.2, Fujifilm Medical Systems). These scans had the central sulcus localised by the two principal investigators on conventional tri-planar volumetric T1 weighted sequences (TE=2.29, TR=2300, 1mm thick slices), using the various anatomical landmarks discussed above. Consensus on the location of the central sulcus was obtained in all cases. A single axial DWI image (obtained in the anterior commissure-posterior commissure plane, B=1000, 4mm thick slices) was then selected for each patient just superior to the subcentral gyrus, thus including the most inferolateral portion of the central sulcus.

These single axial DWI images from each patient were then individually extracted and re-uploaded onto the local PACS research server. Ten readers were recruited, comprising neuroradiologists (3), a neuroradiology fellow (1), and radiology trainees (6). Each was shown an explanatory document (online Appendix A) describing the invisible cortex

feature, showing examples taken from patients not included in the test cohort.

We chose to divide the appearance of the perirolandic cortex into 3 types : normal cortical hyperintensity seen around all parts of the sulcus (Type 1); cortical hyperintensity is lost in the deepest parts of the sulcus (<50% depth, Type 2); cortical hyperintensity is lost in the majority of sulcus (>50% depth, Type 3) (Figure 2). Type 2 and type 3 cortices were considered positive for the "invisible cortex sign". The key challenge is the identification of the sulcus with the least perceptible cortex at its deepest part. In many instances the cortex is isointense to the adjacent white matter. Readers were instructed on how to mark each central sulcus (two per single DWI image) using the annotation tool on PACS. The accuracy in identifying the central sulcus was then compared against the control study i.e. where the two principal investigators had marked the central sulcus on multiple slices of the three-planar T1 volumetric MRI sequences of the same patient tracing it down laterally to the subcentral gyrus. Any sulci which readers had marked as unknown or unsure were considered as incorrect when determining the accuracy in order to minimise bias. We chose to assess the accuracy of multiple readers, instead of quantifying the differences in signal intensity, in order to better apply the "invisible cortex sign" to clinical practice.

At this time, the pattern of cortical signal loss was also graded by the principal investigators according to how much of the sulcal cortex was involved i.e. Type 1, 2 or 3. Differences between the ages of patients in the different types of invisible cortices were determined by one-way ANOVA test and Dunnett T3 post-hoc test analysis (SPSS Statistics version 17). A p-value of <0.05 was considered statistically significant.

Results

Accuracy in Identifying the Central Sulcus Using the Invisible Cortex Sign

The overall mean accuracy for all 10 readers for identifying the central sulcus was 95.5% (σ=3.7) with a range of 89.4 to 99.1%.

There did not appear to be a correlation between the experience of the observer and the number of errors or type of error made in identifying the central sulcus using our method. The highest accuracy of 99.1% was by a first-year radiology resident; the lowest accuracy of 89.4% was by a fifth-year radiology resident; and consultant neuroradiologists' accuracy ranged from 97.7% to 98.1%.

Failure to correctly identify the central sulcus was not randomly distributed, with some central sulci far more difficult to identify than others. Nineteen percent (37/195) of the errors were made on 4.6% (5/108) of the patients. For example, in one patient, 50% of the readers were unable to correctly identify the central sulcus on either side.

Grading Types of Invisible Cortex

Note, that since each DWI image has 2 central sulci (left and right), 216 invisible cortices were graded by each investigator. The number of sulci categorised in each type of invisible cortex as well as the average age in each type is outlined in Table 1. Type 1 cortices were considered to have normal cortical hyperintensity similar to other cortices in the brain. Type 2 and type 3 cortices combined represent the cases in which the "invisible cortex sign" was determined to be present i.e. in 97.7 % (211/216) of cases by Investigator 1 and 95.8% (207/216) of cases by Investigator 2.

Additionally, there were more Type 3 cortices in older individuals (Figure 3). Statistically significant differences between the ages of patients in the different types of invisible cortices was determined by one-way ANOVA (F

(2, 429) = 74.9, p <0.001). Dunnett T3 post hoc test analysis was used as group sizes and variances were not equal. There was a statistically significant difference in the mean age of Type 1 vs Type 2 invisible cortices (p=0.025), Type 1 vs Type 3 invisible cortices (p<0.001), as well as Type 2 vs Type 3 invisible cortices (p<0.001).

Discussion

Our results demonstrate a highly accurate method of identifying the central sulcus which is reproducible amongst observers of variable radiology experience. The small number of errors made were not distributed evenly. Five patients in particular, accounted for 19% of the errors. Review of each of these problematic central sulci revealed one or more of the following causes: poor visualisation of the sulcus in the particular single slice obtained but visible on adjacent slices; partial-voluming due to oblique course of sulcus; unusually asymmetrical location of central sulci presumably leading readers to dismissing the "invisible cortex sign". Retrospective review of the whole DWI scan in these cases, including slices above and below the single study image, determined that the errors would likely be mitigated with the ability to scroll and view the slices above and below.

It is important to emphasise that we have deliberately made the task of identifying the central sulcus artificially difficult by limiting the observers to only one axial DWI slice per patient. Thus, the error rate in our study is almost certainly at the upper limit that should be expected when the whole DWI study is available. Even allowing for this, the accuracy achieved using the "invisible cortex sign" is better than most of the other common landmarks currently in use clinically. The most frequently present sign described in Wagner et al. (the U-sign) was present in 98.9%. However, this required post-processing to generate planar surface reformations from an angled coronal view, and how accurately

radiologists were able to apply this sign in the identification of the central sulcus was not assessed.

The fact that the signal of the perirolandic cortex is different to that of cortex in other gyri is well known and is not just seen on DWI, but also manifests as decreased signal on T2, FLAIR and T2* (6-9). This difference is more apparent with 3T compared to 1.5T for T2-weighted and FLAIR sequences (10). Kaneko et al. also describes a similar sign to our study, of decreased white-grey matter contrast along the central sulcus on T1-weighted 3D inversion recovery fast-spoiled gradient-echo sequence; this may even represent the same sign on a different sequence, but required manual segmentation and computer-assisted post processing for delineation (5).

There are many possible histological and biochemical explanations for the "invisible cortex sign". It is known, for example, that there are differences in the underlying composition and cytoarchitecture of different regions of cortex (11). Specifically, the cellular composition of the cortex is laminar and each layer can have different cell densities and thicknesses. The abundance of myelin staining in each layer can also vary, and these differences can be apparent in the sensorimotor cortex on 7T MRI (12). The boundaries of transition between these different areas of cortex can also be different in different patients, although the cause for this is unclear (11, 12). Dense perineuronal nets in the perirolandic cortex could also have an influence on water diffusion and composition of cytoplasmic and extracellular space (6, 8, 13). Korogi et al. speculated that with a more advanced development of neurons, synaptic density and dendrite formation may cause decreased interstitial water and increased lipid content of the membranes in the cortex, causing T1 and T2 shortening (increased T1-weighted signal and decreased T2-weighted signal); however, this was in the maturing brains of children (14, 15). This theory is also supported by the findings of Ozcan et al., whereby increased DWI

signal of the precentral gyrus became increasingly prevalent in fetuses from 25 weeks gestation onwards, correlating with the progressively increasing sulcation of the fetal brain (16).

It is unclear though, whether the decreased signal of the perirolandic cortices on DWI sequences that we have seen is due to true abnormal diffusion or a T2*-weighted effect. Dincer et al. describes ADC values as quantitatively lower at the primary motor cortex, which would suggest an element of true diffusion restriction, although qualitatively the primary motor cortex appeared to be double layered rather than decreased in signal on DWI sequences (17). Previous studies have also demonstrated SWI and T2-weighted low signal along the perirolandic cortices in patients with amyotrophic lateral sclerosis, speculated to be due to iron accumulation in microglia (9, 18, 19). T2-weighted hypointensity at the motor cortex was seen more frequently in older patients and those with cerebrovascular disease (20). These factors may account for the different types (1 to 3) of cortices we have found in our study, and the trend towards more Type 3 cortices (i.e. more hypointense central sulci cortices) with increasing age, however, as areas of low signal intensity on T2-weighted sequences can be found in a range of central nervous system diseases including Alzheimer's, Parkinson's and cerebral infarction (21) no single aetiology can be inferred from this observation. Also, although these changes were most frequent in the motor cortex, they were also present in the occipital and sensory cortices (21).

Our study is limited by the fact that only one 3T MRI scanner was used for all of the patients. Thus, we have not assessed if the same sign holds for 1.5T MRI scanners, although anecdotally this does appear to be the case. Given that we did not assess ADC maps in our study, future studies could focus on quantitative diffusion characteristics of perirolandic cortex to try and determine the relative T2* and true diffusion contributions to this signal drop. Studies using alternate B-values may also be helpful in

alluding to the histopathological basis for the "invisible cortex sign." Additionally, the "invisible cortex sign" has been investigated only in patients with normal brains, not those with intracranial pathology that could distort the central sulcus. Future studies in patients with pathology may be required to confirm whether the "invisible cortex sign" can indeed help to identify the central sulcus in this context (7, 22).

Conclusion

In conclusion, the "invisible cortex sign", whereby the perirolandic cortices are isointense relative to adjacent white matter on DWI MRI sequences, is a highly accurate method of identifying the inferolateral central sulcus on a single axial slice without needing to rely on the more superior aspects of the sulcus.

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Figure Legends

Figure 1: Appearance of the cortex abutting the central sulcus (arrow head) on T1, T2, fluid attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI), diffusion weighted imaging B=1000 (DWI) and apparent diffusion coefficient (ADC) maps. On all sequences, the perirolandic cortex differs in signal compared to other regional gyri. This is most apparent on DWI and least apparent on ADC and T2.

Figure 2: Appearance of the perirolandic cortex divided into 3 types. Type 1: the cortex is uniformly hyperintense to underlying white matter and is seen around all parts of the sulcus. Type 2: cortical hyperintensity is lost in the deepest parts of the sulcus (<50% depth). Type 3: cortical hyperintensity is lost in the majority of sulcus (>50% depth). The "invisible cortex sign" is deemed to be present in types 2 and 3.

Figure 3: Distribution of type 1, 2 and 3 cortices according to age, demonstrating increasing prevalence in type 3 cortices in older individuals.

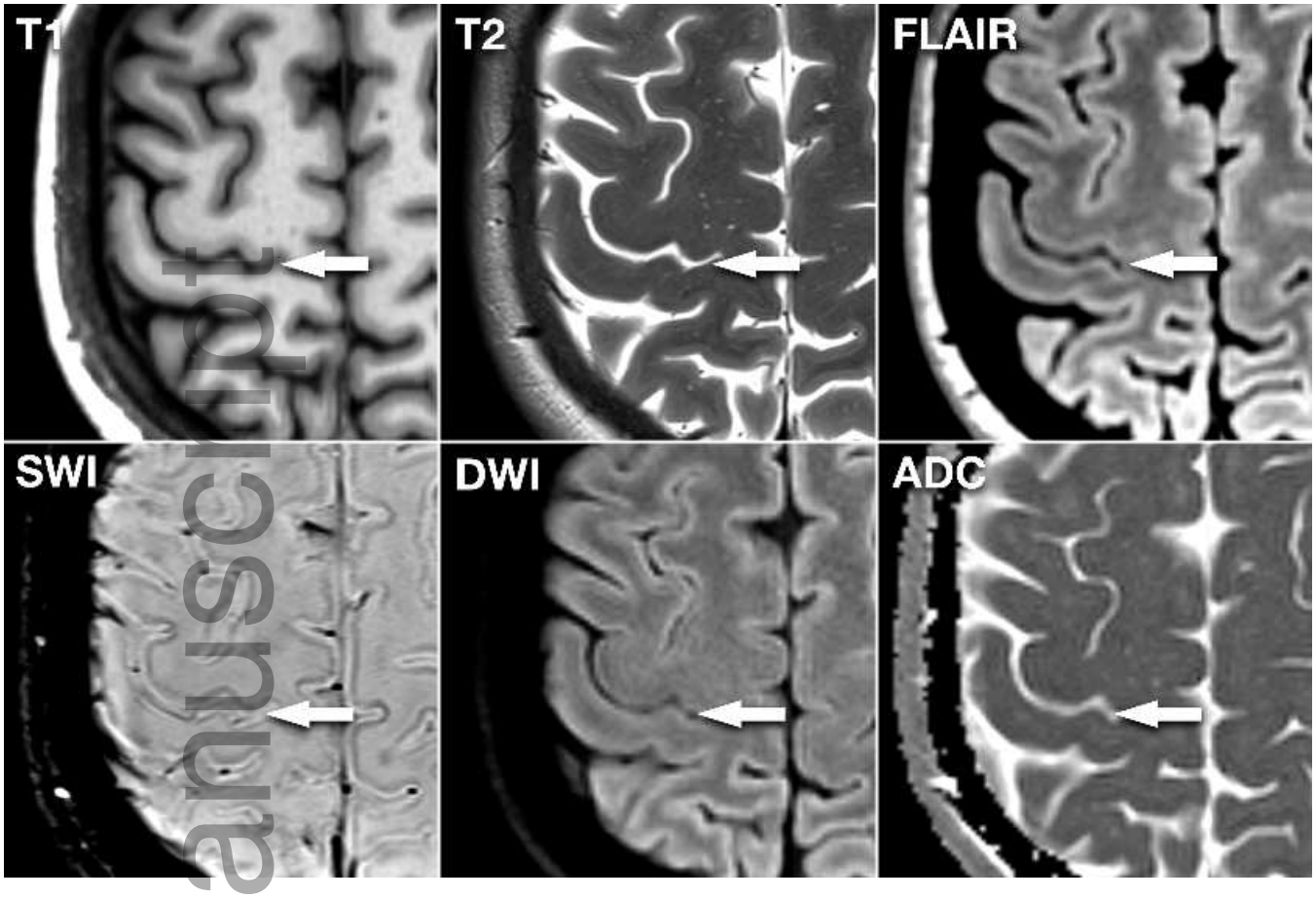
Appendix A

See separate document for "Explanatory Document Given to Readers".

Tables

Table 1: Types of Invisible Cortex and Average Age of Each Type

		Type 1	Type 2	Type 3
Investigator 1	No. of Sulci	5	142	69
	Mean Age in Years (σ)	23.8 (4.0)	33.1 (14.7)	56.7 (14.9)
Investigator 2	No. of Sulci	9	117	90



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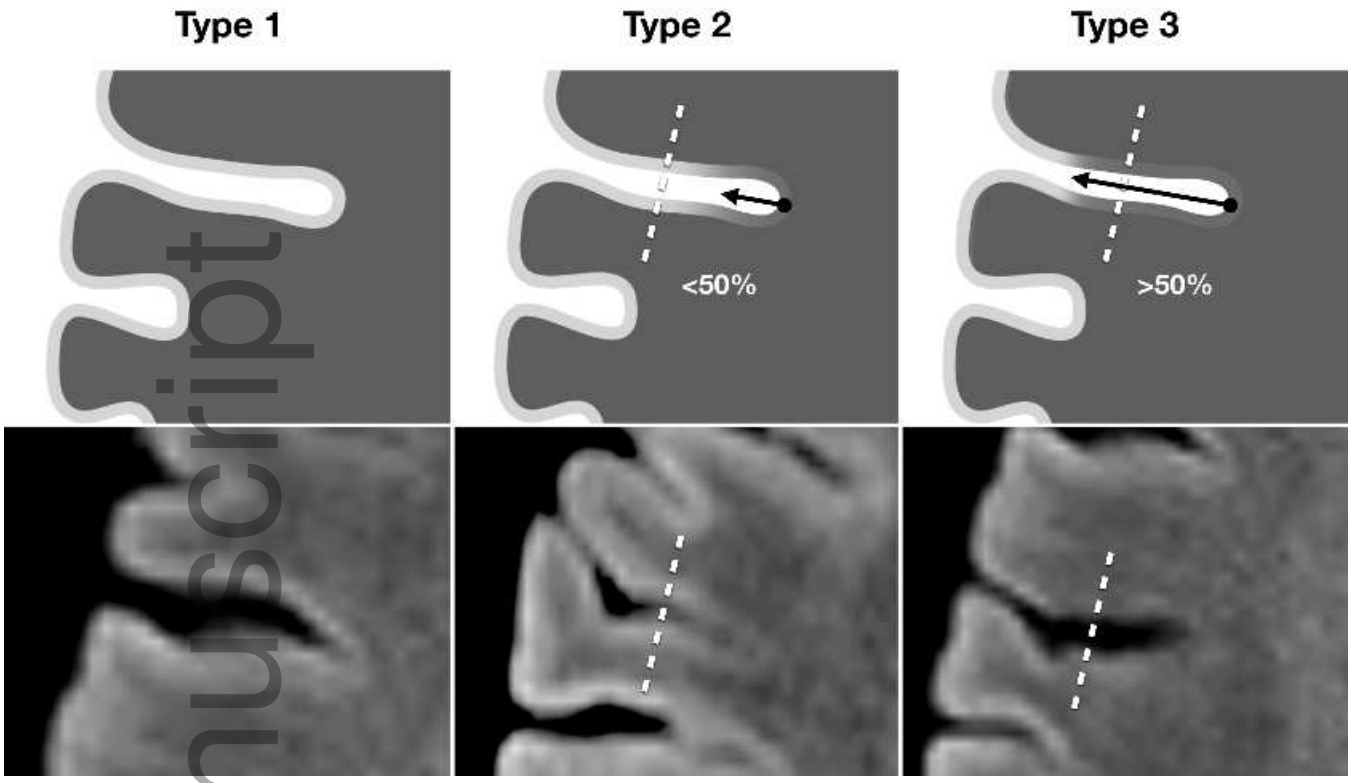

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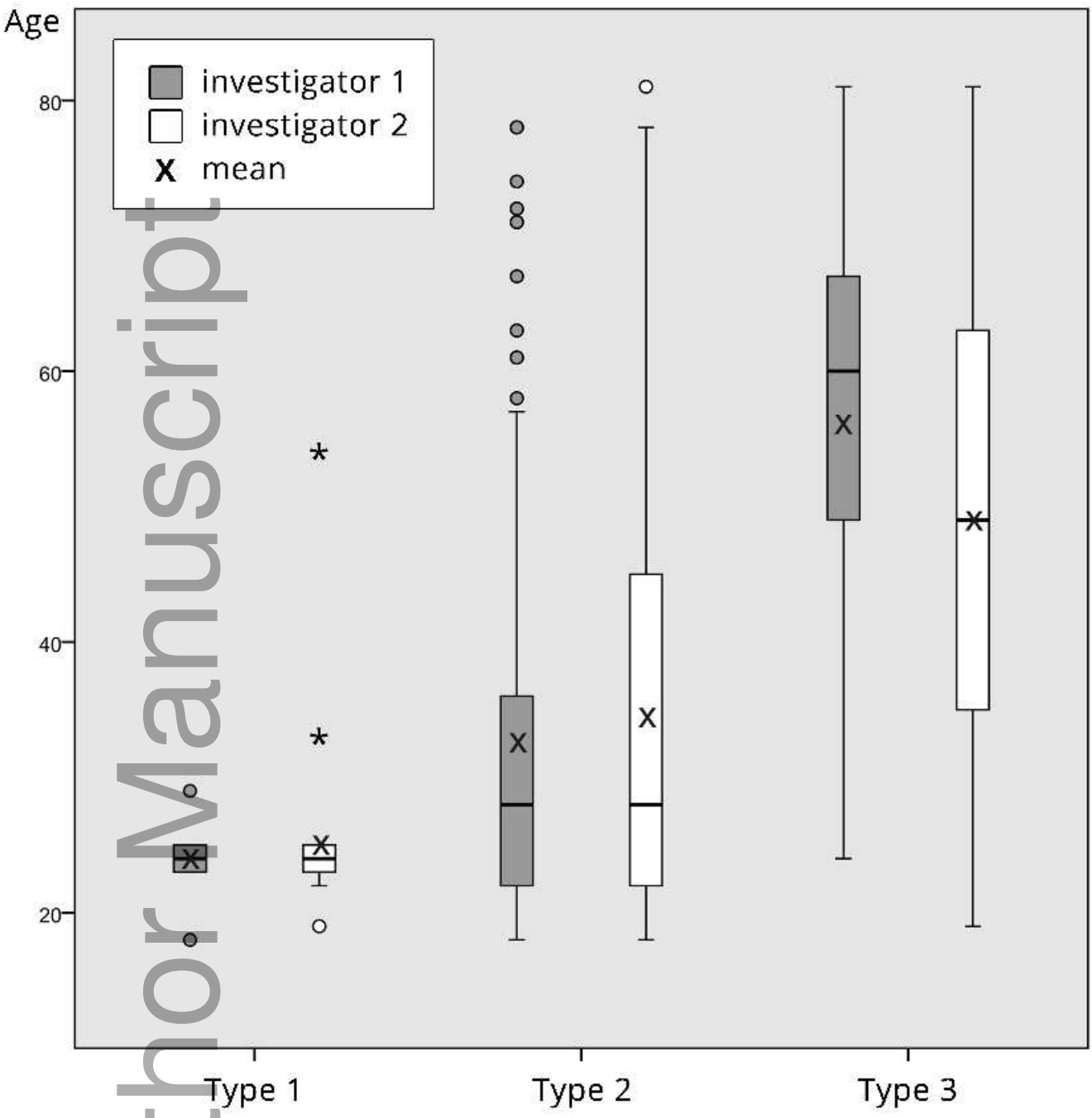

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