ISSN: 2164-5388 Volume 13, Number 1, January 2023

Scientific Research Publishing

Open Journal of Biophysics

ISSN: 2164-5388
9 772164 538002 01

https://www.scirp.org/journal/ojbiphy

Journal Editorial Board

ISSN Print: 2164-5388 ISSN Online: 2164-5396
https://www.scirp.org/journal/ojbiphy

Open Journal of Biophysics, 2023, 13, 1-27
https://www.scirp.org/journal/ojbiphy
ISSN Online: 2164-5396
ISSN Print: 2164-5388

Table of Contents

Volume 13 Number 1 January 2023

Open Journal of Biophysics (OJBIPHY)
Journal Information

SUBSCRIPTIONS

The *Open Journal of Biophysics* (Online at Scientific Research Publishing, https://www.scirp.org/) is published quarterly by Scientific Research Publishing, Inc., USA.

Subscription rates:
Print: $79 per issue.
To subscribe, please contact Journals Subscriptions Department, E-mail: sub@scirp.org

SERVICES

Advertisements
Advertisement Sales Department, E-mail: service@scirp.org

Reprints (minimum quantity 100 copies)
Reprints Co-ordinator, Scientific Research Publishing, Inc., USA.
E-mail: sub@scirp.org

COPYRIGHT

PRODUCTION INFORMATION

For manuscripts that have been accepted for publication, please contact:
E-mail: ojbiphy@scirp.org

Scientific Research Publishing

Open Journal of Biophysics, 2023, 13, 1-13
https://www.scirp.org/journal/ojbiphy
ISSN Online: 2164-5396
ISSN Print: 2164-5388

Contribution of Scintigraphy in the Assessment of Extension of Osteophilic Cancers in Senegal from 2018 to 2021

Olatoundé Herbert Fachinan[1,2], El Hadji Lamine Bathily[2,3], Mamadou Salif Djigo[2,3], Gilles David Houndétoungan[4], Djibrillou Moussa Issoufou[5], Boucar Ndong[3], Kuassi Marcellin Amoussou-Guénou[4], Mamadou Mbodj[2,3]

[1]Institut de Formation en Soins Infirmiers et Obstétricaux, Université de Parakou, Parakou, Bénin
[2]Service de Médecine Nucléaire, Hôpital Général Idrissa Pouye, Dakar, Sénégal
[3]Laboratoire de Biophysique, Médecine Nucléaire, Université Cheikh Anta Diop, Dakar, Sénegal
[4]Unité D'Enseignement et de Recherche de Biophysique et Médecine Nucléaire, Faculté des Sciences de Santé, Université d'Abomey-Calavi, Cotonou, Bénin
[5]Département de Médecine Nucléaire, Institut des Radio-Isotopes, Niamey, Niger
Email: olatounde86@yahoo.fr

How to cite this paper: Fachinan, O.H., Bathily, E.H.L., Djigo, M.S., Houndétoungan, G.D., Issoufou, D.M., Ndong, B., Amoussou-Guénou, K.M. and Mbodj, M. (2023) Contribution of Scintigraphy in the Assessment of Extension of Osteophilic Cancers in Senegal from 2018 to 2021. *Open Journal of Biophysics*, **13**, 1-13.
https://doi.org/10.4236/ojbiphy.2023.131001

Received: September 16, 2022
Accepted: November 1, 2022
Published: November 4, 2022

Abstract

The aim of this study was to highlight the contribution of bone scintigraphy in the assessment of extension of osteophilic cancers in Senegal. This was a retrospective study, with a descriptive and analytical purpose, carried out over a period of four (04) years between January 01, 2018 and December 31, 2021. It focused on the files of patients who underwent bone scintigraphy for extension assessment of an osteophilic cancer during the study period. According to the study, prostate cancer was by far the most representative primary cancer (86.9%). Scintigraphy contributed in 75% of cases (362 cases) with 35% positive scintigraphy and 40% negative scintigraphy. The result was doubtful in 25% of cases (120 cases). The metastatic lesions were located preferentially at the level of the axial skeleton and only one case was of an exclusive appendicular site. More than half of patients with metastases (70%) had a poor prognosis with the SOLOWAY score greater than or equal to II. With the improvement of the nuclear imaging technical platform in Senegal (performance of SPECT/CT examinations), doubtful cases in our sample could be better explored with the advantage of adequate patient care.

Keywords

Bone Scintigraphy, Osteophilic Cancers, Bone Metastases

1. Introduction

Cancer is one of the most common causes of morbidity and mortality worldwide [1]. In Senegal, with an annual incidence of nearly eight thousand cases, cancer is one of the major public health problems because diagnosis is often late and treatment is difficult and costly [2].

The natural evolution of the disease is most often with a spread of cancer cells outside the primary site [3]. Metastatic proliferation follows specific sequential steps from the primary tumor. It is associated with a very reduced survival with an alteration of the quality of life.

Bone is the third most common site of metastatic disease, after the liver and lungs [4]. The cancers most responsible for bone metastases are those of the prostate, breast, thyroid, lungs, kidneys and digestive system [3].

To search for these bone metastases, four medical imaging modalities are commonly used, namely: standard radiography, computed tomography (CT), scintigraphy and magnetic resonance imaging (MRI) [5].

Bone scan remains the most widely used, practical and cost-effective diagnostic technique to assess the whole skeleton for bone metastases since it is more sensitive than other imaging modalities [6].

The aim of the study was to analyze the different scintigraphic aspects in the context of the extension assessment of osteophilic cancers in the nuclear medicine department of the Idrissa Pouye General Hospital in Dakar.

2. Methodology

2.1. Study Method

This was a descriptive and analytical retrospective study. It focused on the files of patients who underwent bone scintigraphy for the assessment of extension of osteophilic cancer in the nuclear medicine department of the Idrissa Pouye General Hospital in Dakar from January 2018 to December 2021. All the studies were performed in the only one functional nuclear medicine service in Senegal.

To collect and exploit the data, we used the patient bone scintigraphy files from the software database (InterViewXP/Médiso), the physical files (clinical observation sheets) of each patient included in the study.

The sampling was exhaustive. For each patient file, the data collected were related to socio-clinical, biological and scintigraphic data. These data were transcribed on a data processing from designed for the study.

2.2. Technique for Performing the Scintigraphic Examination

Bone scintigraphy was done according to the classic protocol on the whole body: anterior and posterior surfaces in order to obtain images of the entire skeleton. For exploration, a diphosphonate derivate, hydroxymethylene diphosphonate (HMDP) labeled with technetium 99 m (^{99m}Tc) was injected intravenously with an activity of 8 to 10 MBq/kg, without exceeding 1200 MBq. The acquisition was carried out in patients in supine position on the examination table, three hours later, thanks to a scan of the whole body by a SPECT Médiso gamma camera with a high-resolution low-energy collimator at a speed of 15 cm per minute.

3. Results

A total of 482 bone scans were performed as part of an extension assessment from 2018 to 2021 at General Idrissa Pouye Hospital in Dakar.

3.1. General Data

3.1.1. Years of Achievement

The number of bone scans for staging of osteophilic cancer in Senegal has been constantly increasing during the study period, ranging from 70 patients received in 2018 to 174 patients received in 2021.

On average, 120 patients have undergone bone scintigraphy each year to search for secondary bone locations.

3.1.2. Primary Cancers Concerned

Table 1 presents the organ site of the primary cancer of the patients seen for research of secondary bone localizations.

The other primary cancers were as follows: four (4) cases of osteosarcoma, two (2) cases of bladder tumours, one (1) case of tongue tumour, one (1) case of ovarian cancer, one (1) case of cervical cancer and one (1) case of kidney cancer.

It should be noted that according to the D'Amico classification, scintigraphy was justified (intermediate risk and high risk of bone metastases) in almost all patients with prostate cancer (96.2%).

3.1.3. Ages of Patients

The mean age of the patients was 65.69 years and extremes of 17 and 88 years. Table 2 reports the age of the patients according to the primary cancer developed.

3.2. Scintigraphic Data

3.2.1. Indications for Bone Scan

Indications for bone scintigraphy were largely represented by the completion of extension workup (94.8% of cases). There were 19 cases (3.9%) of control scintigraphy and only 6 (1.2%) cases of biochemical recurrence.

Table 1. Distribution of patients according to the organ site of the primary cancer.

Primitive Cancer	Frequency	Percentage (%)
Prostate	**419**	**86.9**
Breast	29	6.0
Thyroïde	24	5.0
Other	10	2.1
Total	482	100.0

Table 2. Age distribution of patients according to the primary cancer developed.

Primary cancer	Ages				
	Mean	Median	Standard deviation	Minimum	Maximum
Prostate	68.22	68.00	7.299	49	88
Breast	49.41	48.00	12.037	28	72
Thyroid	46.54	46.50	13.565	17	68
Other	53.10	57.00	12.600	26	65
Total	65.69	67.00	10.470	17	88

3.2.2. Contribution of Scintigraphy

The scintigraphy was contributory in 75.1% (362 patients) of the cases, with 169 patients (35.1%) presenting bone metastases (positive scintigraphy) against 193 patients (40.0%) with no bone metastases (negative scintigraphy).

The result was doubtful (inconclusive) in 120 patients (24.9%).

- **Primary cancer and scintigraphic results**

Figure 1 shows the distribution of the primary cancer site organ according to the presence of bone metastases.

- **PSA level and presence of metastases**

Figure 2 shows the relationship between the PSA level in ng/ml and the presence or an absence of bone metastases.

Of the 419 patients with prostate cancer, those with bone metastases on scintigraphy had a mean PSA level of 171.35 ng/ml, a median of 106.5 ng/ml and extremes of 10.5 and 850 ng/ml.

Patients without metastases had a mean PSA level of 35.1 ng/ml, a median of 28 ng/ml and extremes of 4.9 and 100 ng/ml.

For those with a dubious scintigraphy, the average PSA level was 60.1 ng/ml, the median level 54 ng/ml and extremes of 6.59 and 180 ng/ml.

- **Histology of prostate cancer and presence of metastases**

In our study, 133 out of 137 (97.1%) patients with metastases had a Gleason score greater than or equal to 7. Of the 53 patients with a Gleason score of 7, 47 had a Gleason score of (4 + 3) versus (3 + 4) for 6 of the patients.

- **Histology of breast cancer and presence of metastases**

Of the 17 patients with bone metastases, 14 (82.4%) had infiltrating carcinoma and 3 (17.6%) had ductal carcinoma in situ.

- **Histology of thyroid cancer and presence of metastases**

Among the 9 patients with thyroid cancer and bone metastases, 8 (88.9%) had papillary carcinoma and only one (11.1%) had vesicular carcinoma.

3.2.3. Topography of Metastatic Bone Lesions

In the study, of the patients who presented with bone metastases, 147 (87.5%) presented with multiple metastatic lesions and 21 (12.5%) presented with a solitary lesion.

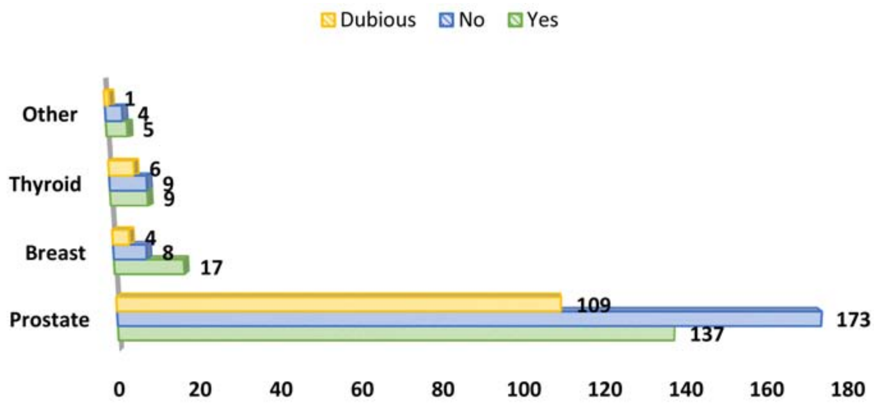


Figure 1. Primary cancer and scintigraphic results.

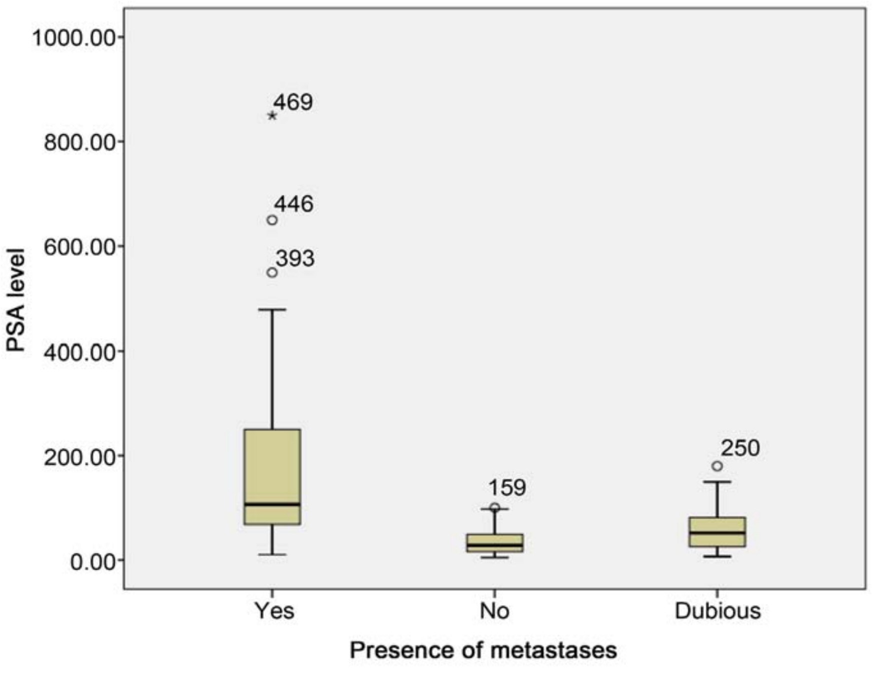


Figure 2. PSA level in ng/ml and presence of metastases.

- **topography of lesions**

Figure 3 reports the sites of bone metastases.

NB: the case of an exclusive localization in the appendicular skeleton from a patient that had a prostate cancer.

- **Precision of the topography at the level of the axial skeleton**

For patients with bone metastases, our study showed in decreasing order that 124 patients out of 168 (73.8%) had a spinal location, 117 patients out of 168 (69.6%) at the costal grill, 99 patients out of 168 (58.9%) at the pelvic girdle, 88 out of 168 patients (52.4%) at the sternum and 48 out of 168 patients (28.6%) at the chest girdle.

3.2.4. Types of Bone Lesions

The bone metastatic lesions found were raising of uptake in 154 cases (91.7%);

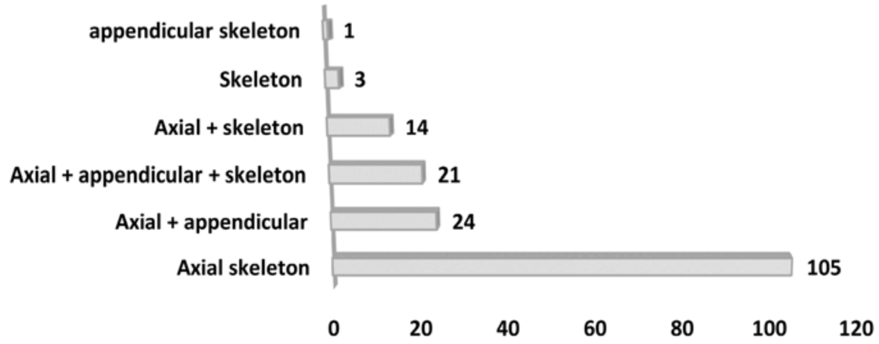


Figure 3. Sites of bone metastases.

mixed (association of high uptake and lytic lesions) in 12 cases (7.1%) and lytic lesions in 2 cases (1.2%). Both cases of lytic lesions were found in patients with thyroid cancer.

3.2.5. Quantification of Bone Involvement

The SOLOWAY score was used to quantify metastatic bone lesions.

51 of 169 patients (30%) had grade I (less than six bone metastases); 57 of 169 patients (34%) had grade II (between six and 20 bone metastases); 42 patients out of 169 (25%) had grade III (more than 20 bone metastases but less than a Superscan) and 19 patients out of 169 (11%) had grade IV (Superscan).

3.3. Some Images of Different Bone Scan Models

Figures 4-6 show some images of different bone scan models from our study.

4. Discussion

4.1. General Data

4.1.1. Years of Achievement

The number of bone scans for extension assessment of osteophilic cancer in Senegal has been steadily increasing from 2018 to 2021. On average, 120 patients have benefited from bone scans each year to search for secondary bone locations. This testifies not only to the increasing evolution of the incidence of cancers in Senegal [1], but also to the increasing visibility of the nuclear medicine department of the Idrissa Pouye General Hospital in Dakar.

4.1.2. Primary Cancers Concerned

Despite being the fourth most common cancer in Senegal after cancer of the cervix, breast and liver [2], prostate cancer, according to our study, was the most representative primary cancer. This cancer is by far the most common primary cancer in our sample because of the proximity (location) of the department that provides the most bone scans for bone metastases. This is the urology department of the Idrissa Pouye General Hospital in Dakar. The physicians of this department are well informed about the services offered by our nuclear medicine department.

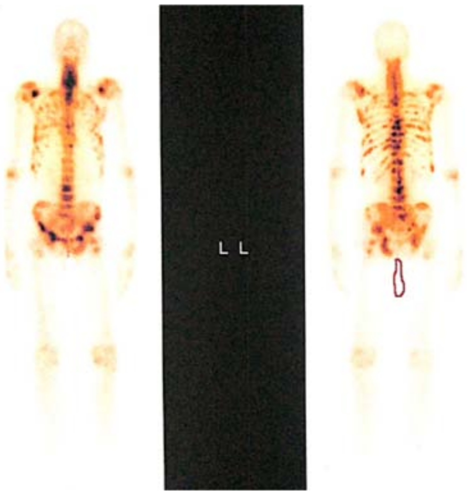


Figure 4. Whole body Bone scan performed in an 81-year-old with prostate adenocarcinoma. Description of Figure 4: Whole body Bone scan performed in an 81-year-old with prostate adenocarcinoma. There are multiple focal and intense hyperfixations in the cervical and thoracolumbar spin, anterior and posterior costal arches, sternum and pelvis (sacrum, iliac wings, pubic symphysis, ilio and ischi-pubic branches) compatible with metastases bones. We conclude with a scintigraphic picture of metastatic super bone scan.

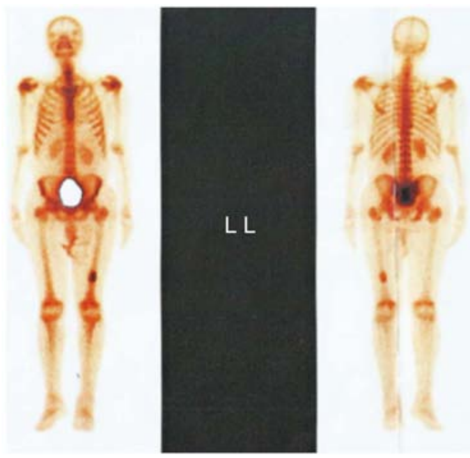


Figure 5. Whole body bone scan performed in an 81-year-old with prostate adenocarcinoma. Description of Figure 5: Whole body bone scan performed in an 81-year-old with prostate adenocarcinoma. There are focal hyperfixation in the distal diaphyseal of the left femur suggestive of solitary secondary bone localization (or osteosarcoma?). We therefore conclude that there is a scintigraphic aspect of solitary secondary left femoral bone localization, without ruling out osteosarcoma of the left femur.

It will be necessary to extend and strengthen information to other health structures in order to serve the whole country for the well-being of patients.

4.1.3. Ages of the Patients

The average age of the patients with prostate cancer in our study was 68.22 years and extremes of 49 and 88 years. The mean age of the patients is comparable to those reported in the literature, in particular those observed by Ndong and al (66.71 years) [7], Jalloh and al (65.61 years) [8]. For these authors, prostate cancer

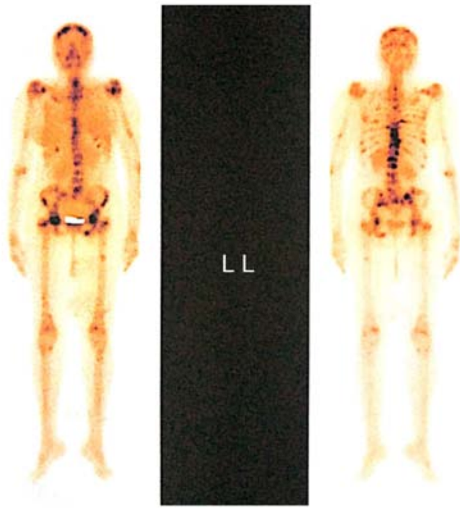


Figure 6. Whole body bone scan performed in 45-year-old patient with left breast carcinoma. Description of **Figure 6**: Whole body bone scan performed in 45-year-old patient with left breast carcinoma. There are multiple focal and intense hyperfixations localized in the skull, cervical and thoraco-lumbar spine, sternum, anterior and posterior costal arches, pelvis (iliac wings, sacrum, ilio and ischio-pubic branch) and left femur, compatible with bone metastases. We conclude that there is a scintigraphic appearance of multiple secondary bone localisations realizing diffuse malignant osteosis.

is a disease of the elderly.

Regarding patients with breast cancer, their mean age in our study was 49.41 years and extremes of 28 and 72 years. Some authors have found similar results, notably El Ajmi *et al*. (51.59 years) [9], Diop *et al*. (46.9 years) [10], Mayi-Tsonga *et al*. (48 years) [11].

As for thyroid cancer, the mean age in our series was 46.54 years and extremes of 17 and 68 years. Williams et al had noted in their study that the incidence of thyroid cancer increases in early adulthood and decreases in people over 75 years [12]. The same findings have also been made by some authors [13] [14].

4.2. Scan Results

4.2.1. Indications and Contribution of Scintigraphy

Indications for bone scintigraphy of patients were largely represented by the completion of extension work-up (94.8% of cases). There were 19 cases (3.9%) of control scintigraphy and only 6 cases (1.2%) of biochemical recurrence. Punnen & Al have noted that several indications require medical imaging in the management of cancerous pathologies [15]. Among the indications, they found nearly 30% biochemical recurrence in their sample [15].

In principle, nuclear imaging in the management of cancerous pathologies is not only performed for the purpose of extension assessment. The lack of an adequate technical platform in Senegal would justify these results. Several authors have argued that the use of 18F-FCholine PET/CT is currently recommended for the search and localization of recurrences in patients with biochemical relapse [16] [17]. Others have gone further by demonstrating the importance of identifying, by 68Ga-PSMA-11 PET/CT imaging, the locations of recurrence in order to propose optimal locoregional or systematic treatment. They found a higher positivity rate than 18F-Fcholine PET/CT imaging [18] [19].

Scintigraphy contributed in 75% of cases (362 cases). The result was doubtful in 25% of cases (120 cases). It revealed 35% positive scintigraphy and 40% negative scintigraphy.

For patients with prostate cancer, scintigraphy was positive in 32.7% of cases. Ndong and collaborators found a similar result (33.33% positive scintigraphy) in their study [7].

Regarding patients with breast cancer, scintigraphy was positive in 58.6% of cases. Diop and colleagues found 30% positive scintigraphy [10]; a result lower than ours.

As for patients with thyroid cancer, scintigraphy was positive in 37.5% of cases. Similar results have been found in the literature [20].

With the improvement of the nuclear imaging technical platform in Senegal (realization of SPECT/CT and PET/CT examinations), doubtful cases could be better explored with the advantage of adequate patient care.

4.2.2. PSA Blood Level and Positive Scintigraphy

Of the 419 patients with prostate cancer, those with bone metastases on scintigraphy had a mean PSA level of 171.35 ng/ml, a median of 106.5 ng/ml and extremes of 10.5 and 850 ng/ml. Patients without metastases had a mean PSA level of 35.1 ng/ml, a median of 28 ng/ml and extremes of 4.9 and 100 ng/ml.

Already described in the literature, the blood level of PSA is correlated with the presence of metastases [7] [21]. Thus, Jemal and collaborators had shown that a PSA level above 10 ng/ml was indicative of localized prostate cancer; a level greater than 50 ng/ml indicated extra-prostatic involvement in 80% of cases and finally a level greater than 100 ng/ml proved systematic extra-prostatic involvement [21].

4.2.3. Primary Cancer Histology and Positive Scintigraphy

The Gleason score is a histo-prognostic score characterizing the degree of tumor differentiation, and an essential prognostic factor in the management of prostate cancer. It is obtained by adding the two histological grades ranging from 1 to 5, of the most represented cancers [22]. In our study, 133 out of 137 patients (97.1%) with metastases had a Gleason score greater than or equal to 7. Ndong and collaborators in Senegal found in 2011 results slightly lower than ours. In fact, 80% of the patients in their series with a positive scintigraphy had a Gleason score greater than or equal to 7 [7].

For the 53 patients with a Gleason score equal to 7, there were 47 (82.6%) who presented a score (4 + 3) and therefore a poorer prognosis. This subdivision is widely integrated into the therapeutic decision in the case of localized prostate cancer [23].

The histology of the breast cancer of the patients in the study is represented by infiltrating carcinoma in 58.6% of cases and by ductal carcinoma in situ in 41.4% of cases. However, of the 17 breast cancer patients with bone metastases, 14 (82.4%) had infiltrating carcinoma and only 3 (17.6%) had ductal carcinoma in situ. The analytical study revealed that there is a statistically significant link between the histological type and the presence or absence of metastases ($P = 0.00 < 0.05$). In infiltrating breast carcinomas, malignant cells spread to nearby tissues which may promote distant spread [9].

Among the 9 patients with thyroid cancer and bone metastases, 8 (88.9%) had papillary carcinoma and only one (11.1%) had vesicular carcinoma. In the literature, papillary carcinoma appears to be the most representative cancer of thyroid cancers [24]. However, a correlation between histological types and the presence or absence of bone metastases has not been demonstrated.

4.2.4. Topography of Metastatic Bone Lesions

Multiple metastatic lesions are mainly represented (87.5% of cases of metastases) in our sample. Some authors have also found the predominance of multiple lesions in their respective study [7] [10]. In our study, the metastatic lesions were preferentially located in the axial skeleton and only one case was exclusively appendicular. Our results are comparable to those of the literature [7] [10]. Indeed, tumor cells are localized secondarily by preference to the most richly vascularized parts of the skeleton such as the hematopoietic bone marrow of the axial skeleton, the upper extremities of the humeri, femurs and tibiae [25].

Furthermore, our study showed in decreasing order that 124 patients out of 168 (73.8%) had a spinal localization, 117 patients out of 168 (69.6%) at the level of the costal grill, 99 patients out of 168 (58.9%) at the pelvic girdle, 88 patients out of 168 (52.4%) at the level of the sternum and 48 patients out of 168 (28.6%) at the thoracic girdle. These results are almost identical to those found by some authors in the literature [7] [10].

4.2.5. Types of Bone Lesions

Bone metastases in our study were largely represented by hyperfixing lesions. The results are comparable to those found by Diop and colleagues [10]. Bone hyperfixation is suggestive of metastasis, but unequivocal because of its non-specificity [10]. Indeed, there was a differential diagnosis between metastases and benign pathologies which are linked to significant bone remodeling, especially when these foci of osteoblastic hyperfixation were unique and/or were located at the level of particular anatomical regions (for example near joints) [10].

Only two patients in our study presented osteolytic lesions. Lytic lesions are exceptional, linked to increased osteoclast activity and are often found in cases of thyroid or breast cancer [3].

4.2.6. Quantification of Bone Involvement

The SOLOWAY score was used to quantify metastatic bone lesions. This quantification technique revealed that more than half of patients with metastases (70%) had a poor prognosis with a grade greater than or equal to II. This meant that these patients consulted late or were poorly monitored on an outpatient basis, as we mentioned above. The same observation has been made in the literature [7] [9].

For patients with prostate cancer, the mean and median of the PSA level increased with the grades of the SOLOWAY score. Already described in the literature, there is an increasing relationship between SOLOWAY grades and PSA level [7] [26].

5. Conclusions

Bone scintigraphy occupies a place of choice in the detection of bone metastases, due to its high sensitivity. It can determine the prognosis by taking into account the number of locations, the topography and the metastatic bone tumor volume which are predictive factors of the patient's survival time.

Its low specificity raises the indication of an improvement of the technical platform of nuclear imaging in Senegal (performance of SPECT/CT, PET/CT examinations). Thus, the doubtful cases of our sample could be better explored with the advantage of adequate patient management.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Bouri, N.V., Ba, O., Dieme, J.L., Mbengue, M., *et al.* (2017) État des lieux du registre des tumeurs au Sénégal: Bilan à 6 ans d'enregistrement en ligne. *Revue des Maladies Respiratoires*, **34**, A75. https://doi.org/10.1016/j.rmr.2016.10.156

[3] Lipton, A. (2004) Pathophysiology of Bone Metastases: How This Knowledge May Lead to Therapeutic Intervention. *The Journal of Supportive Oncology*, **2**, 205-213.

[4] Macedo, F., Ladeira, K., Pinho, F., Saraiva, N., *et al.* (2017) Bone Metastases: An Overview. *Oncology Reviews*, **11**, 43-49. https://doi.org/10.4081/oncol.2017.321

[5] Rybak, L.D. and Rosenthal, D.I. (2001) Radiological Imaging for the Diagnosis of Bone Metastases. *Quarterly Journal of Nuclear Medicine and Molecular Imaging*, **45**, 53-64.

[6] Pamedo, H., Marx, C., Ebert, A., Kreft, B., Ko, Y., *et al.* (2014) Whole Body SPECT/CT for Bone Scintigraphy: Diagnostic Value and Effect on Patient Management in Oncologic Patients. *European Journal of Nuclear Medicine and Molecular Imaging*, **41**, 59-67. https://doi.org/10.1007/s00259-013-2532-6

[7] Ndong, B., Mbodj, M., Mbaye, G., Ndoye, O., Bathily, E.H.A.L., *et al.* (2012) Place de la scintigraphie osseuse dans le bilan d'extension des métastases des cancers de la prostate au Sénégal: Étude préliminaire à propos de 45 cas. *Médecine Nucléaire*, **36**, 586-590. https://doi.org/10.1016/j.mednuc.2012.05.012

[8] Jalloh, M., Thia, W.G., Bathily, E.H.A.L., Dial, C., Ndoye, M., *et al.* (2018) Corréla-

tion entre score de Gleason biopsique et métastases osseuses à la scintigraphie dans le cancer de la prostate. *Uro'Andro*, **1**, 501-508.

[9] El Ajmi, W., Ben Hmida, O., Limam, K., Hammami, H. and Sellem, A. (2020) Cancer du sein en Tunisie: Profil épidémiologique et dépistage des métastases osseuses. *Médecine Nucléaire*, **44**, 107-135. https://doi.org/10.1016/j.mednuc.2020.01.046

[10] Diop, O., Ndong, B., Bathily, E.A.L., Sow, D.W., Senghor, R.S., *et al.* (2014) Place de la scintigraphie osseuse dans le bilan d'extension des métastases osseuses du cancer du sein au Sénégal: Étude préliminaire à propos de 40 cas. *Revue Cames Sante*, **2**, 57-62.

[11] Mayi-Tsonga, S., Belembago, E., Meyé, J., *et al.* (2009) Les cancers du sein au Gabon: Aspects épidémiologique, diagnostic et thérapeutique. *Journal Africain du Cancer*, **1**, 11-15. https://doi.org/10.1007/s12558-008-0003-y

[12] Williams, D. (2015) Thyroid Growth and Cancer. *European Thyroid Journal*, **4**, 164-173. https://doi.org/10.1159/000437263

[13] Davies, L. and Welch, H.G. (2014) Current Thyroid Cancer Trends in the United States. *JAMA Otolaryngology—Head & Neck Surgery*, **140**, 317-322. https://doi.org/10.1001/jamaoto.2014.1

[14] Zhu, C., Zheng, T., Kilfoy, B.A., *et al.* (2009) A Birth Cohort Analysis of the Incidence of Papillary Thyroid Carcinoma in the United States, 1973-2004. *Thyroid*, **19**, 1061-1066. https://doi.org/10.1089/thy.2008.0342

[15] Punnen, S., Cooperberg, M.R., D'Amico, A.V., Karakiewicz, P.I., Moul, J.W., *et al.* (2013) Management of Biochemical Recurrence after Primary Treatment of Prostate Cancer: A Systematic Review of the Literature. *European Urology*, **64**, 905-915. https://doi.org/10.1016/j.eururo.2013.05.025

[16] Boubaker, A., Houzard, C., Zouhair, A., Got, P. and Orcurto, M.V. (2011) Cancer de la prostate: Utilité de la TEP-TDM à la 18F-fluorocholine. *Médecine Nucléaire*, **35**, 446-454. https://doi.org/10.1016/j.mednuc.2011.05.010

[17] Husarik, D.B., Miralbell, R., Dubs, M., John, H., Giger, O.T., *et al.* (2008) Evaluation of [18F]-choline PET/CT for Staging and Restaging of Prostate Cancer. *European Journal of Nuclear Medicine and Molecular Imaging*, **35**, 253-263. https://doi.org/10.1007/s00259-007-0552-9

[18] Gauthé, M., Belissant, O., Girard, A., Zhang, Y.J., Ohnona, J., *et al.* (2017) TEP/TDM et récidive biologique d'adénocarcinome prostatique: apport du 68Ga-PSMA-11 lorsque la 18F-fluorocholine n'est pas contributive. *Progrès en Urologie*, **27**, 474-481. https://doi.org/10.1016/j.purol.2017.04.004

[19] Verburg, F.A., Pfister, D., Heidenreich, A., Vogg, A., Drude, N.I., *et al.* (2016) Extent of Disease in Recurrent Prostate Cancer Determined by [68Ga]PSMA-HBED-CC PET/CT in Relation to PSA Levels, PSA Doubling Time and Gleason Score. *European Journal of Nuclear Medicine and Molecular Imaging*, **43**, 397-403. https://doi.org/10.1007/s00259-015-3240-1

[20] Muresan, M.M., Olivier, P. and Leclere, J. (2008) Bone Metastases from Differentiated Thyroid Carcinoma. *Endocrine-Related Cancer*, **15**, 37-49. https://doi.org/10.1677/ERC-07-0229

[21] Jemal, A., Siegel, R., Ward, E., Murray, T., Xu, J. and Thun, M. (2007) Cancer Statistics, 2007. *CA*: *A Cancer Journal for Clinicians*, **57**, 43-66. https://doi.org/10.3322/canjclin.57.1.43

[22] Rozet, F., Cornu, J.N., Cussenot, O., Fromont, G. and Hennequin, C. (2010) Cancers de la prostate cliniquement localisée à haut risque de progression. *Bulletin du Cancer*, **97**, 1517-1536.

[23] Joly, F. and Henry-Amar, M. (2007) Facteurs pronostiques du cancer de la prostate localisé, localement évolué et en phase métastatique. *Bulletin du Cancer*, **94**, 35-43.

[24] Matta-Coelho, C., Simoes-Pereira, J., Vilar, H. and Leite, V. (2019) Bone Metastases from Thyroid Carcinoma of Follicular Origin: A Single Institutional Experience. *European Thyroid Journal*, **8**, 96-101. https://doi.org/10.1159/000494719

[25] Paycha, F. and Richard, B. (2001) Exploration scintigraphique du squelette. *Encyclopédie médico-chirurgicale*, **30**, 480-490.

[26] Soloway, M.S., Hardeman, S.W., Hickey, D., Raymond, J., Todd, B., Soloway, S. and Moinuddin, M. (1988) Stratification of Patients with Metastatic Prostate Cancer Based on Extent of Disease on Initial Bone Scan. *Cancer*, **61**, 195-202. https://doi.org/10.1002/1097-0142(19880101)61:1<195::AID-CNCR2820610133>3.0.CO;2-Y

Scientific Research Publishing

Open Journal of Biophysics, 2023, 13, 14-27
https://www.scirp.org/journal/ojbiphy
ISSN Online: 2164-5396
ISSN Print: 2164-5388

Statistical Analysis on Gender Difference in Neural Activity for Spatial Ability Tasks

Sung-Ho Kim[1*], Namgil Lee[2], Chang-Hyun Park[3]

[1]Department of Mathematical Sciences, Korea Advanced Institute of Science and Technology, Daejeon, South Korea
[2]Department of Information Statistics, Kangwon National University, Chuncheon, South Korea
[3]Center for Neuroprosthetics and Brain Mind Institute, Swiss Federal Institute of Technology(EPFL), Geneva, Switzeland
Email: *sung-ho.kim@kaist.edu

How to cite this paper: Kim, S.-H., Lee, N. and Park, C.-H. (2023) Statistical Analysis on Gender Difference in Neural Activity for Spatial Ability Tasks. *Open Journal of Biophysics*, **13**, 14-27.
https://doi.org/10.4236/ojbiphy.2023.131002

Received: September 28, 2022
Accepted: November 7, 2022
Published: November 10, 2022

Abstract

Gender differences are investigated from the viewpoint of cognitive neuroscience in the domain of spatial ability. Five task types of geometric problems are used for the collection of task-evoked fMRI data. Although there was no gender-difference in task performance, we found gender differences in neural activity. Some of the important gender differences that we found are 1) that there are far more joint neuro-activations among the brain regions, co-activations or reverse-activations, in males than in females, 2) that the two types of joint activations were nearly half and half in females while it was mostly co-activations in males, 3) that males tend to have more co-activations in the left hemisphere than expected while females tend to have more between-hemisphere co-activations than expected, and 4) that the left-right pairs of BA's are more highly associated than average for males while they are far less associated than average for females.

Keywords

Cross-Correlation, Functional Magnetic Resonance Imaging, Co-Activation and Reverse-Activation, Between and Within Hemisphere

1. Introduction

Spatial ability is the ability that is employed for executing cognitive tasks such as generating, storing, retrieving, and transforming visuo-spatial information. This ability is known to produce robust gender differences favoring males [1]-[7]. It is also reported in the literature that males usually perform better on mental rotation tasks than females [8]-[16]. As correlates of gender differences in spatial ability, biological factors such as sex hormones associated with the phase of the menstrual cycle [13] [17] [18] [19] [20] or the ratio of the 2nd to 4th finger length [14] [21] [22] [23], bodily measures [24], and structural brain morphology [25], and environmental factors such as gender role socialization [26] [27] and the level of education [1] [28] [29] [30] have been inspected. Although some supporting hypotheses for gender differences in spatial ability, such as an evolutionary hypothesis [31] [32] [33] [34] [35], a gender similarity hypothesis [36] [37], and a functional lateralization hypothesis [38]-[45] were proposed, the issue of gender difference in spatial ability is yet wide open.

In this study, we analyzed functional magnetic resonance imaging (fMRI) data of task performances and explored gender differences in spatial ability by using five task types of spatial ability in an effort to refine the neurocognitive understanding of spatial ability. The five task types consist of picture completion (PC), mental rotation (MR), surface development (SD), aperture passing (AP), and hole punching (HP). We found gender differences in neural correlates and activations in response to the five task types. We also saw a gender difference in the functional relationship among brain regions.

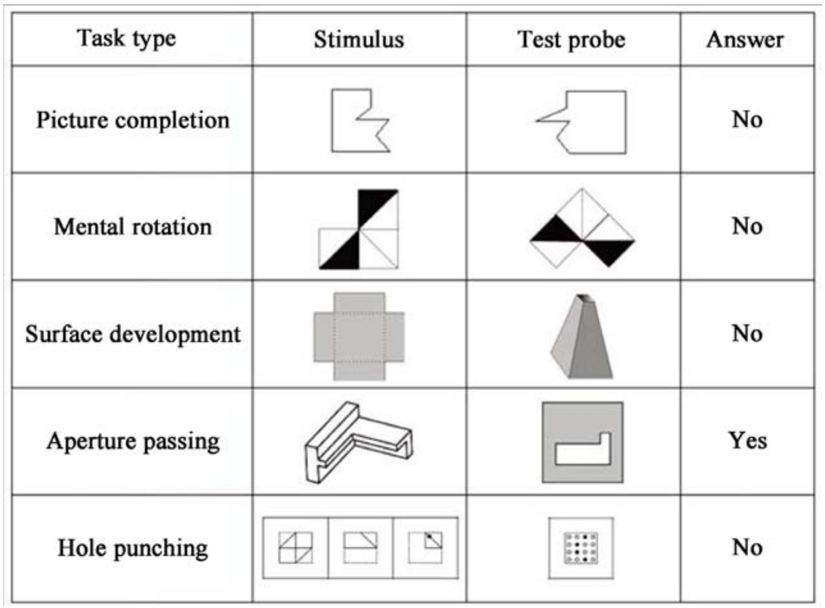
2. Method

2.1. Participants

61 young healthy undergraduate students (27 males and 34 females) participated in the study. They were recruited by announcements on the bulletin boards of a local university and all of them majored in natural sciences or engineering. All the participants reported no history of psychiatric or neurological abnormality and submitted the signed informed consent forms.

2.2. Data Acquisition and Task Types

fMRI data were acquired from an ISOL FORTE scanner (ISOL Technology, Gyeonggi, Korea) operating at 3 Tesla. A total of 177 whole-brain images were collected using a T2*-weighted single-shot echo-planar imaging (EPI) sequence (repetition time (TR) = 3000 msec, echo time (TE) = 35 msec, number of slices = 36, slice thickness = 3 mm, matrix size = 64 × 64, the field of view = 220 mm × 220 mm). Subjects performed 5 types of spatial ability tasks during the scanning. In a block designed experiment, 15 problem sets (5 task types × 3 problem sets) were presented in a random order to each subject. A set of problems were presented at regular intervals (21 seconds) after instructions on how to solve problems (6 seconds). Fixations were provided before a subsequent problem set (9 seconds). As shown in **Figure 1**, each problem was displayed in two figure frames, one for a stimulus and the other for a test probe. If the test probe corresponded appropriately to the stimulus figure, that is, 1) in picture completion if the test probe fitted the stimulus, 2) in mental rotation if the test probe was rotated to match the stimulus, 3) in surface development if the test probe was constructed by folding the stimulus, 4) in aperture passing if the test probe was a projection from the stimulus, and 5) in hole punching if the stimulus was acquired by



Task type	Stimulus	Test probe	Answer
Picture completion			No
Mental rotation			No
Surface development			No
Aperture passing			Yes
Hole punching			No

Figure 1. Sample problems of the five task types.

unfolding the test probe, a subject was supposed to answer 'Yes' or 'No' by pressing the left or right mouse button, respectively. The overall performance of the tasks was measured as discriminability, that is, hit rate minus false alarm rate. The cognitive complexity of the five task types of spatial ability was measured by task scores.

2.3. fMRI Data Analysis

Preprocessing and statistical analysis of the fMRI data were carried out using the SPM8 software (Wellcome Trust Centre for Neuroimaging, University College London, London, UK). The preprocessing steps included spatial realignment to the mean volume of a series of images, normalization into the same coordinate frame as the MNI-template brain, and smoothing using a Gaussian filter of 8 mm FWHM. The fMRI data were then analyzed statistically for each participant and the analysis results were used for random-effects analysis. In random-effects analysis, we used a factorial design for repeated measures ANOVA with gender as a between-group factor and task type as a within-group factor. We checked for an interaction effect between gender and task type and for consistent gender differences in neural activation across the five task types. In all statistical inferences, we determined the statistical significance at the height threshold of an uncorrected p-value less than 0.001 and the cluster extent threshold of more than ten voxels.

3. Results

3.1. Trend in Task Scores

We saw no significant gender difference in the mean of the task scores with the p-value, 0.052. For more detailed description of the difference, the 95% simultaneous confidence intervals of the difference are given in Table 1 and the boxplots of the task scores in Figure 2. For convenience' sake, we will label the five task types, PC, MR, SD, AP, and HP, respectively, by 1, 2, ···, 5.

We can apparently see a trend of the mean scores across the task types as displayed in panel (a) of Figure 3. The mean scores are decreasing in the order of PC, MR, AP, SD, and HP. The difference among the score means is displayed in panel (b) by grouping. The task scores in the same parentheses suggest no significant difference between them at the significance level 0.05. For both sexes, task type 1 and each of task types 3, 4, and 5 are significantly different in the context of task scores, and so are task types 2 and 5. The score grouping is slightly different between males and females in that task types 4 (AP) and 5 (HP) are significantly different in females while they are not in males. As for males,,

Table 1. The 95% simultaneous confidence intervals of the differences of means, $\mu_M - \mu_F$.

Task type	Lower limit	Upper limit
1 (PC)	−1.83	3.57
2 (MR)	−1.96	6.32
3 (SD)	−2.69	6.61
4 (AP)	−2.88	3.87
5 (HP)	−0.08	7.77

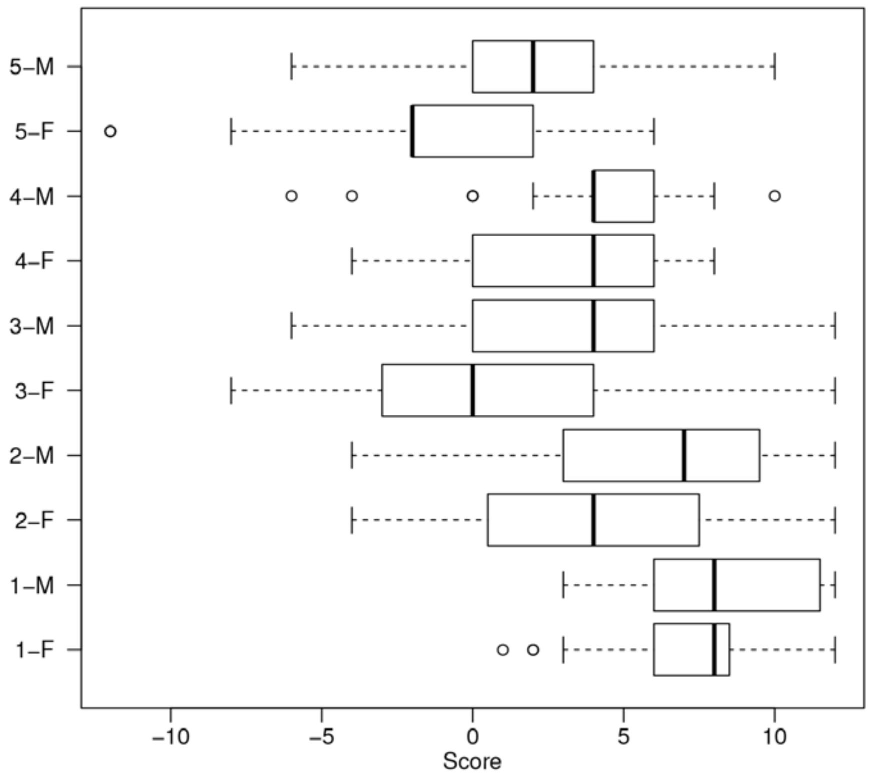
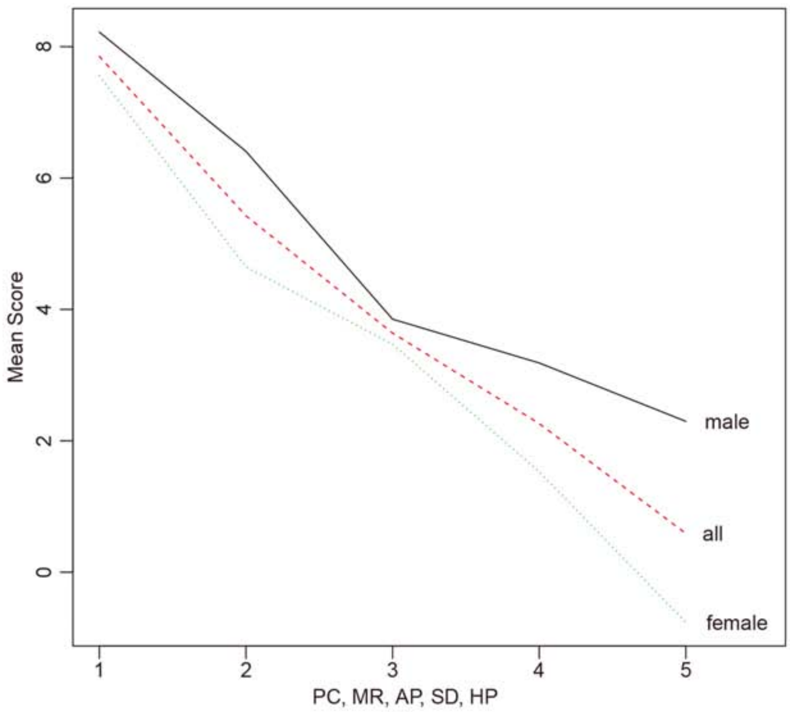


Figure 2. Boxplots of task scores.



(a)

Sex	Grouping
Male	(PC, MR), (MR, AP, SD), (AP, SD, HP)
Female	(PC, MR), (MR, AP, SD), (SD, HP)

(b)

Figure 3. Comparison of the mean task scores between male and female for the 5 task types. In panel (b), the task types in the same group (in parentheses) are regarded as of equal mean task scores at the significance level $\alpha = 0.05$. (a) Mean task scores; (b) Multiple comparison of mean task scores.

task types 3, 4, and 5 belong to the same score group while only task types 3 and 5 (*i.e.*, SD and HP) belong to the same score group for females.

3.2. Gender Difference in Neural Activity for All the Tasks

While there was no significant gender difference in task scores, we could see significant gender differences in neural activities. Across the five task types, males showed higher activations consistently in the occipital cortex (OC) (BA 17, 18, 19), left prefrontal cortex (PFC) (BA 44) and posterior parietal cortex (PPC) (BA 7, 23), whereas females showed higher activations consistently in the left PPC (BA 40). In repeated measures ANOVA, an interaction effect between gender and task type was shown in the OC.

3.3. Cross-Correlations of Neural Activation

Let X_{kt} denote the activity level at brain region k in response to task type t. Then the cross-correlation $corr\left(X_{kt}, X_{lu}\right) = 0$ means, under the Gaussian assumption, that the activity level at brain region k in response to task type t is independent of the activity level at brain region l in response to task type u. In other words, a high activity level at brain region k in solving a problem of task type t does not necessarily imply a high (or low) activity level at brain region l in solving a problem of task type u.

Figure 4 summarises the cross-correlations of the activity levels among the 82

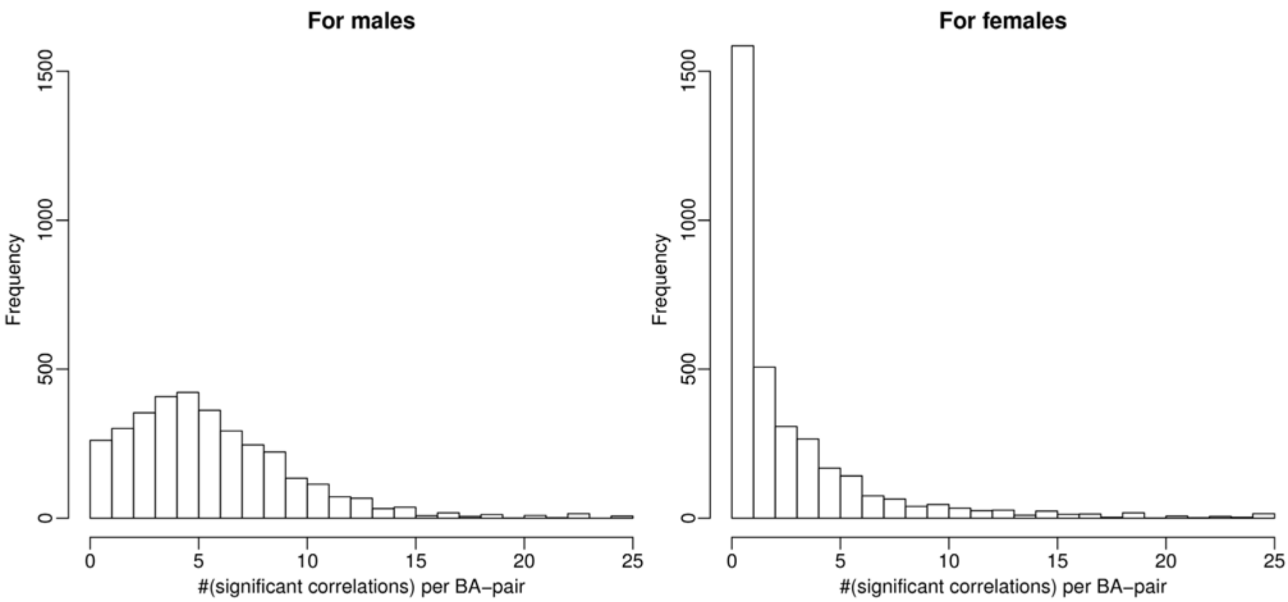


Figure 4. Gender-difference in cross-correlations of the brain activitivation in response to the 5 task types across the 82 BA's. For each BA-pair, the number (n_{kl}) of the task-type pairs are counted whose correlations are significant ($\alpha = 0.05$), and the distribution of $n_{kl}, 1 \le k \le l \le 82$, is given in histogram for each sex.

Table 2. Frequency table of $n_{kl} \le 7$.

Sex	n_{kl}							
	0	1	2	3	4	5	6	7
F	1585	507	308	266	168	142	75	64
M	261	301	354	408	422	362	293	246

Brodmann areas (BA's). For each BA-pair, BA's k and l ($1 \le k, l \le 82$), we counted the number n_{kl} of the task-type pairs for which the brain activity levels are correlated significantly. Note that $0 \le n_{kl} \le 25$ for all k, l. The histograms in the figure show the distribution of n_{kl}. We can see a dramatic gender difference in the distribution. A part of the frequency table is given in **Table 2** as a zoom-in for the histograms. This apparent difference indicates that brain regions are more associated functionally in males than in females. The number of the BA-pairs for which $n_{kl} = 0$ is 1585 which is about a half (48%) of the total number of BA-pairs (=3321). If we consider up to the numbers of $n_{kl} \le 1$, it is 2092 (63%) for females and 562 (17%) for males. This is a strong indication that there is a far less functional association among the brain regions for females than for males. We may interpret this as that: males are more co-operative in brain activity than females as far as the problem solving of geometric problems is concerned.

Another question we were interested in was if there is a stronger association between the left-right counterparts of BA than between every other pair of BA's. We can see a gender difference in **Table 3**. As for the male, the association between the left-right counterparts of BA is a more often occurrence than it is among

Table 3. Quantiles of n_{kl} for two types of BA pairs. (a) For males; (b) For females.

(a)

Brain regions	Proportion (%)								
	10	20	30	40	50	60	70	80	90
Left-right pairs	5	7	9	10	11	13	14	17	19
All the other pairs	2	3	4	4	5	6	7	8	10

(b)

Brain regions	Proportion (%)								
	10	20	30	40	50	60	70	80	90
Left-right pairs	0	0	0	1	1	1	2	2	5
All the other pairs	0	0	1	1	2	2	3	4	7

the other pairs of BA's. The asymptotic *z*-score of the Mann-Whitney-Wilcoxon (MWW) test [46] is 6.79 (with its upper tail probability near 0), which strongly indicates a higher left-right association of BA's than the average of the associations among the BA's. The phenomenon is quite a contrary for females, as can be seen in the table. The left-right association is shown to be weaker than average with the asymptotic *z*-score of the MWW test −4.40 (with its lower tail probability near 0). In a nutshell, there are more pairwise left-right BA associations than average in males while there are fewer of them than average in females. We need a little bit of prudence here in that the MWW test is used under the assumption that n_{kl}'s are independent of each other. As a matter of fact, they may not be independent. We however used this test as an approximate surrogate to measure the difference between the two pair types of BA's, left-right counterpart pairs and the other type of pairs.

So far we have investigated significance of the association without regard to the sign of the correlation. If the correlation is positive, we may interpret the association of a pair of BA's as co-activation; otherwise, as reverse-activation. **Table 4** summarizes the analysis result of the pairwise activation patterns. The patterns are surprisingly contrasting between males and females. Among the associations between BA's, they are mostly due to co-activation for males while they are divided nearly half and half between the two types of activities for females. This result seems to be well in tune with the findings by [47] in the context of neural processing efficiency.

We were also interested in whether there are more co-activations or reverse-activations between hemispheres than within hemispheres or vice versa. To further investigate in this line, we took each of the numbers in **Table 4** into three pieces, one corresponding to the mutual activations of the BA's in the left hemisphere, another in the right hemisphere, and a third between hemispheres. This refinement is summarized in **Table 5**. For instance, the value 1518 for males in **Table 4** is broken into three pieces, 409, 746, and 363. 409 BA-pairs co-activate

Table 4. Co-activation and reverse-activation counts of BA's. The numbers are of the BA-pairs for each task type which are significant at the significance level 0.05. "+" ("-") stands for co-activation (reverse-activation).

Sex	Task type									
	1		2		3		4		5	
	−	+	−	+	−	+	−	+	−	+
M	26	1518	0	2408	2	1637	0	2253	0	2249
F	178	196	180	171	152	156	175	172	180	183

Table 5. Co-activation and reverse-activation counts of BA's between and within hemispheres. The numbers are of the BA-pairs for each task type which are significant at the significance level 0.05. "L" and "R" stand for the left and right hemispheres, respectively, and "Between" for "between hemisphere".

Task type	Male			Female					
	Co-activation			Co-activation			Reverse-activation		
	L	Between	R	L	Between	R	L	Between	R
1	409↑	746	363	35	115↑	46	41	84	53
2	608	1225	575	34	93	44	52	76↓	52
3	455↑	788↓	394	28	95↑	33	37	70	45
4	606↑	1124	523	38	107↑	27	39	92	44
5	589	1114↓	546	34	108↑	41	40	85	55

Note (1) The ↑ in the "L" column means that its value significantly larger than its counterpart in the "R" column at the significance level $\alpha = 0.05$. (2) The ↑ in the "Between" column means that the number of the between-hemisphere BA-pairs which co-activate (or reverse-activate) are significantly larger (↓ for smaller) than the number of the within-hemisphere BA-pairs which co-activate (or reverse-activate) at $\alpha = 0.05$.

in the left (L) hemisphere, 363 BA-pairs in the right (R) hemisphere, and 746 between-hemisphere BA-pairs. We ignored the reverse-activation for males since there were only 28 such cases.

It is obvious in **Table 5** that, in males, there are a larger or equal number of co-activations in the left hemisphere than expected. On the other hand, the between-hemisphere co-activations occur at least as often as expected in females. There are no significant differences in the number of reverse-activations in females except that the between-hemisphere reverse-activation occurs less often than expected for task type 2. In a nutshell, males tend to use the left hemisphere more often than expected and, as for females, between-hemisphere co-activations are more often than expected.

The two types of joint activations in females are displayed in **Figure 5**, which is obtained by applying the modelling method as proposed in [48]. Co-activation BA-pairs are connected by red lines and reverse-activation BA-pairs by blue lines. We can see in the figure that the two types of joint activations occur over almost the same brain regions each other and that some brain regions are functionally connected with other regions more in co-activation than in reverse-activation and vice versa. It is obvious in the figure that a brain region co-activates with another region while it reverse-activates with a third. As a visual aid, we added a figure of the joint activations for the five task types in **Figure 6**.

To sum up the analysis results of correlations, as long as the problem solving of geometric problems are concerned, 1) brain regions are far more associated functionally in males than females (**Table 2**), 2) the left-right pairs of BA's are more highly associated than average for males while they are far less associated than average for females (**Table 3**), 3) the association between brain regions are mostly due to co-activation for males while, for females, only half of the associations are due to co-activation and the other half by reverse-activation (**Table 4**), and 4) males tend to have more co-activations in the left hemisphere than expected while females tend to have more between-hemisphere co-activations than expected (**Table 5**).

4. Concluding Remarks

In the correlation analysis, we tried to investigate functional connectivity among

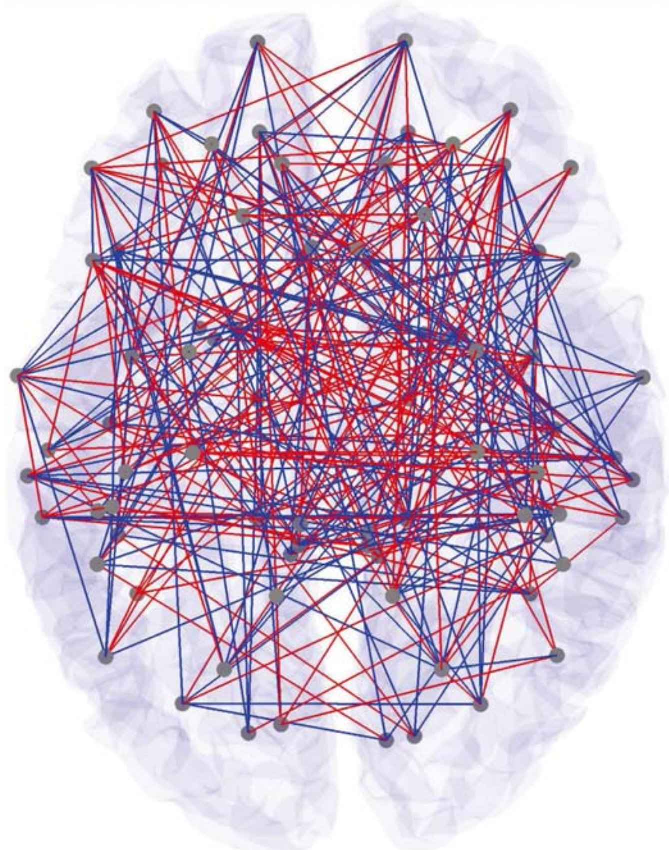


Figure 5. Inferior view of co-activation (in red) and reverse-activation (in blue) between brain areas of a female participant.

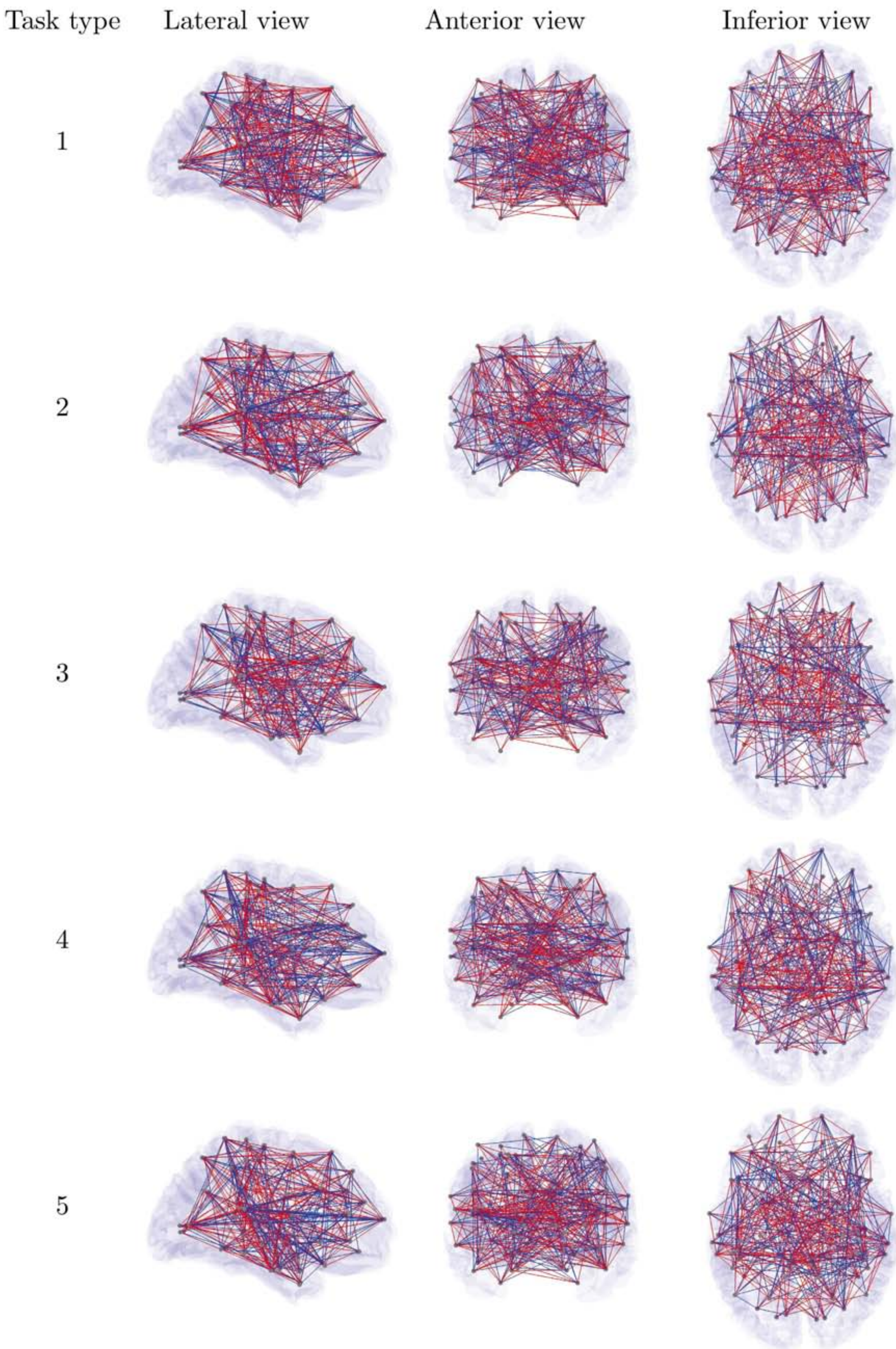


Figure 6. Co-activation (in red) and reverse-activation (in blue) graphs for females from three viewpoints, lateral, anterior, and inferior.

brain regions from two viewpoints. In one of them, we counted the number (n_{kl}) of task type pairs for which a certain pair of BA's, say BA's k and l, are correlated significantly. For each $k \neq l$, $0 \leq n_{kl} \leq 25$. A larger n_{kl} can be interpreted as a stronger correlation between BA's k and l. There was no significant functional connectivity for nearly half (48%) of the BA-pairs for females while it is only 8% for males. This is a global look at functional connectivity without regard to the task type.

A refined description of the functional connectivity for each task type is that males are found to have more or as many co-activations of BA's in the left hemisphere as expected, while females are found to have more or as many co-activations between hemispheres as expected. This result is well in tune with the gender difference in the structural connectome of the brain found in [49]. As for the patterns of functional connectivity, the connectivity is shown to be via co-activation for males while it is divided almost half and half into co-activation and reverse-activation for females.

The result of this work is limited in interpretation in the sense that the data for this work is from college students majoring in natural sciences or engineering. However, it is worthwhile to note that male and female students could get the same performance scores on spatial ability tasks while the neural activity pattern was quite contrasting between males and females, as was found in the paper.

Acknowledgements

The authors wish to thank Prof. Ah-Young Kim of Ewha University, South Korea for providing a set of problems in Geometry that were used for data collection. The research was supported by a grant from the National Research Foundation of the Republic of Korea (Grant No: 2020R1A2C1A0100876711).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Contreras, M.J., Colom, R., Shih, P.C., Álava, M.J. and Santacreu, J. (2001) Dynamic Spatial Performance: Sex and Educational Differences. *Personality and Individual Differences*, **30**, 117-126. https://doi.org/10.1016/S0191-8869(00)00015-5

[2] Contreras, M.J., Rubio, V.J., Pena, D., Colom, R. and Santacreu, J. (2007) Sex Differences in Dynamic Spatial Ability: The Unsolved Question of Performance Factors. *Memory and Cognition*, **35**, 297-303. https://doi.org/10.3758/BF03193450

[3] Crucian, G.P. and Berenbaum, S.A. (1998) Sex Differences in Right Hemisphere Tasks. *Brain and Cognition*, **36**, 377-389. https://doi.org/10.1006/brcg.1998.0999

[4] Lawton, C.A. and Hatcher, D.W. (2005) Gender Differences in Integration of Images in Visuospatial Memory. *Sex Roles*, **53**, 717-725. https://doi.org/10.1007/s11199-005-7736-1

[5] Ruggiero, G., Sergi, I. and Iachini, T. (2008) Gender Differences in Remembering and Inferring Spatial Distances. *Memory*, **16**, 821-835.

https://doi.org/10.1080/09658210802307695

[6] Vecchi, T. and Girelli, L. (1998) Gender Differences in Visuo-Spatial Processing: The Importance of Distinguishing between Passive Storage and Active Manipulation. *Acta Psychologica*, **99**, 1-16. https://doi.org/10.1016/S0001-6918(97)00052-8

[7] Weiss, E., Siedentopf, C.M., Hofer, A., Deisenhammer, E.A., Hoptman, M.J., Kremser, C., Golaszewski, S., Felber, S., Fleischhacker, W.W. and Delazer, M. (2003) Sex Differences in Brain Activation Pattern during a Visuospatial Cognitive Task: A Functional Magnetic Resonance Imaging Study in Healthy Volunteers. *Neuroscience Letters*, **344**, 169-172. https://doi.org/10.1016/S0304-3940(03)00406-3

[8] Collins, D.W. and Kimura, D. (1997) A Large Sex Difference on a Two-Dimensional Mental Rotation Task. *Behavioral Neuroscience*, **111**, 845-849. https://doi.org/10.1037/0735-7044.111.4.845

[9] Geiser, C., Lehmann, W., Corth, M. and Eid, M. (2008) Quantitative and Qualitative Change in Children's Mental Rotation Performance. *Learning and Individual Differences*, **18**, 419-429. https://doi.org/10.1016/j.lindif.2007.09.001

[10] Halari, R., Sharma, T., Hines, M. andrew, C., Simmons, A. and Kumari, V. (2006) Comparable fMRI Activity with Differential Behavioural Performance on Mental Rotation and Overt Verbal Fluency Tasks in Healthy Men and Women. *Experimental Brain Research*, **169**, 1-14. https://doi.org/10.1007/s00221-005-0118-7

[11] Hirnstein, M., Bayer, U. and Hausmann, M. (2009) Sex-Specific Response Strategies in Mental Rotation. *Learning and Individual Differences*, **19**, 225-228. https://doi.org/10.1016/j.lindif.2008.11.006

[12] Kerkman, D.D., Wise, J.C. and Harwood, E.A. (2000) Impossible "Mental Rotation" Problems: A Mismeasure of Women's Spatial Abilities? *Learning and Individual Differences*, **12**, 253-269. https://doi.org/10.1016/S1041-6080(01)00039-5

[13] Kozaki, T. and Yasukouchi, A. (2009) Sex Differences on Components of Mental Rotation at Different Menstrual Phases. *International Journal of Neuroscience*, **119**, 59-67. https://doi.org/10.1080/00207450802480101

[14] Peters, M., Manning, J.T. and Reimers, S. (2007) The Effects of Sex, Sexual Orientation, and Digit Ratio (2D:4D) on Mental Rotation Performance. *Archives of Sexual Behavior*, **36**, 251-260. https://doi.org/10.1007/s10508-006-9166-8

[15] Arrighi, L. and Hausmann, M. (2022) Spatial Anxiety and Self-Confidence Mediate Sex/Gender Differences in Mental Rotation. *Learning & Memory*, **2022**, 312-320. https://doi.org/10.1101/lm.053596.122

[16] Rahe, M. and Jansen, P. (2022) Sex Differences in Mental Rotation: The Role of Stereotyped Material, Perceived Performance and Extrinsic Spatial Ability. *Journal of Cognitive Psychology*, **34**, 400-409. https://doi.org/10.1080/20445911.2021.2011896

[17] Chabanne, V., Peruch, P. and Thinus-Blanc, C. (2004) Sex Differences and Women's Hormonal Cycle Effects on Spatial Performance in a Virtual Environment Navigation Task. *Cahiers de Psychologie Cognitive*, **22**, 351-375.

[18] McCormick, C.M. and Teillon, S.M. (2001) Menstrual Cycle Variation in Spatial Ability: Relation to Salivary Cortisol Levels. *Hormones and Behavior*, **39**, 29-38. https://doi.org/10.1006/hbeh.2000.1636

[19] Schoning, S., Engelien, A., Kugel, H., Schafer, S., Schiffbauer, H., Zwitserlood, P., Pletziger, E., Beizai, P., Kersting, A., Ohrmann, P., Greb, R.R., Lehmann, W., Heindel, W., Arolt, V. and Konrad, C. (2007) Functional Anatomy of Visuo-Spatial Working Memory during Mental Rotation Is Influenced by Sex, Menstrual Cycle, and Sex Steroid Hormones. *Neuropsychologia*, **45**, 3203-3214. https://doi.org/10.1016/j.neuropsychologia.2007.06.011

[20] Bernal, A. and Paolieri, D. (2022) The Influence of Estradiol and Progesterone on Neurocognition during Three Phases of the Menstrual Cycle: Modulating Factors. *Behavioral Brain Research*, **417**, Article ID: 113593. https://doi.org/10.1016/j.bbr.2021.113593

[21] Kempel, P., Gohlke, B., Klempau, J., Zinsberger, P., Reuter, M. and Hennig, J. (2005) Second-to-Fourth Digit Length, Testosterone and Spatial Ability. *Intelligence*, **33**, 215-230. https://doi.org/10.1016/j.intell.2004.11.004

[22] Putz, D.A., Gaulin, S.J.C., Sporter, R.J. and McBurney, D.H. (2004) Sex Hormones and Finger Length—What Does 2D:4D Indicate? *Evolution and Human Behavior*, **25**, 182-199. https://doi.org/10.1016/j.evolhumbehav.2004.03.005

[23] Sanders, G., Bereczkei, T., Csatho, A. and Manning, J. (2005) The Ratio of the 2nd to 4th Finger Length Predicts Spatial Ability in Men but Not Women. *Cortex*, **41**, 789-795. https://doi.org/10.1016/S0010-9452(08)70297-1

[24] Tan, U., Okuyan, M., Albayrak, T. and Akgun, A. (2003) Sex Differences in Verbal and Spatial Ability Reconsidered in Relation to Body Size, Lung Volume, and Sex Hormones. *Perceptual and Motor Skills*, **96**, 1347-1360. https://doi.org/10.2466/pms.2003.96.3c.1347

[25] Koscik, T., O'Leary, D., Moser, D.J. andreasen, N.C. and Nopoulos, P. (2009) Sex Differences in Parietal Lobe Morphology: Relationship to Mental Rotation Performance. *Brain and Cognition*, **69**, 451-459. https://doi.org/10.1016/j.bandc.2008.09.004

[26] Schug, M.G., Barhorst-Cates, E., Stefunucci, J., Creem-Regehr, S., Olsen, A.P. and Cashdan, E. (2022) Childhood Experience Reduces Gender Differences in Patial Abilities: A Cross-Cultural Study. *Cognitive Science*, **46**, e13096. https://doi.org/10.1111/cogs.13096

[27] Saucier, D.M., McCreary, D.R. and Saxberg, J.K.J. (2002) Does Gender Role Socialization Mediate Sex Differences in Mental Rotations? *Personality and Individual Differences*, **32**, 1101-1111. https://doi.org/10.1016/S0191-8869(01)00106-4

[28] Peters, M., Lehmann, W., Takahira, S., Takeuchi, Y. and Jordan, K. (2006) Mental Rotation Test Performance in Four Cross-Cultural Samples (N = 3367): Overall Sex Differences and the Role of Academic Program in Performance. Cortex, **42**, 1005-1014. https://doi.org/10.1016/S0010-9452(08)70206-5

[29] Van Exel, E., Gussekloo, J., De Craen, A.J.M., Bootsma-van Der Wiel, A., Houx, P., Knook, D.L. and Westendorp, R.G.J. (2001) Cognitive Function in the Oldest Old: Women Perform Better than Men. *Journal of Neurology Neurosurgery and Psychiatry*, **71**, 29-32. https://doi.org/10.1136/jnnp.71.1.29

[30] Weiss, E.M., Kemmler, G., Deisenhammer, E.A., Fleischhacker, W.W. and Delazer, M. (2003) Sex Differences in Cognitive Functions. *Personality and Individual Differences*, **35**, 863-875. https://doi.org/10.1016/S0191-8869(02)00288-X

[31] Ecuyer-Dab, I. and Robert, M. (2004) Have Sex Differences in Spatial Ability Evolved from Male Competition for Mating and Female Concern for Survival? *Cognition*, **91**, 221-257. https://doi.org/10.1016/j.cognition.2003.09.007

[32] Gaulin, S.J.C. and Fitzgerald, R.W. (1989) Sexual Selection for Spatial-Learning Ability. *Animal Behaviour*, **37**, 322-331. https://doi.org/10.1016/0003-3472(89)90121-8

[33] Jones, C.M., Braithwaite, V.A. and Healy, S.D. (2003) The Evolution of Sex Differences in Spatial Ability. *Behavioral Neuroscience*, **117**, 403-411. https://doi.org/10.1037/0735-7044.117.3.403

[34] Silverman, I., Choi, J., Mackewn, A., Fisher, M., Moro, J. and Olshansky, E. (2000) Evolved Mechanisms Underlying Wayfinding: Further Studies on the Hunter-Gatherer

Theory of Spatial Sex Differences. *Evolution and Human Behavior*, **21**, 201-213. https://doi.org/10.1016/S1090-5138(00)00036-2

[35] Geary, D.C. (2022) Spatial Ability as a Distinct Domain of Human Cognition: An Evolutionary Perspective. *Intelligence*, **90**, Article ID: 101616. https://doi.org/10.1016/j.intell.2021.101616

[36] Hyde, J.S. (2005) The Gender Similarities Hypothesis. *American Psychologist*, **60**, 581-592. https://doi.org/10.1037/0003-066X.60.6.581

[37] Hyde, J.S. (2007) New Directions in the Study of Gender Similarities and Differences. *Current Directions in Psychological Science*, **16**, 259-263. https://doi.org/10.1111/j.1467-8721.2007.00516.x

[38] Levy, J. (1976) Cerebral Lateralization and Spatial Ability. *Behavior Genetics*, **6**, 171-188. https://doi.org/10.1007/BF01067147

[39] Lewis, R.S. and Kamptner, N.L. (1987) Sex Differences in Spatial Task Performance of Patients with and without Unilateral Cerebral Lesions. *Brain and Cognition*, **6**, 142-152. https://doi.org/10.1016/0278-2626(87)90115-1

[40] McGlone, J. (1980) Sex Differences in Human Brain Asymmetry: A Critical Survey. *Behavioral and Brain Sciences*, **3**, 215-263. https://doi.org/10.1017/S0140525X00004398

[41] McGlone, J. and Kertesz, A. (1973) Sex Differences in Cerebral Processing of Visuospatial Tasks. *Cortex*, **9**, 313-320. https://doi.org/10.1016/S0010-9452(73)80009-7

[42] Rilea, S.L. (2008) A Lateralization of Function Approach to Sex Differences in Spatial Ability: A Reexamination. *Brain and Cognition*, **67**, 168-182. https://doi.org/10.1016/j.bandc.2008.01.001

[43] Rilea, S.L., Roskos-Ewoldsen, B. and Boles, D. (2004) Sex Differences in Spatial Ability: A Lateralization of Function Approach. *Brain and Cognition*, **56**, 332-343. https://doi.org/10.1016/j.bandc.2004.09.002

[44] Siegel-Hinson, R.I. and McKeever, W.F. (2002) Hemispheric Specialisation, Spatial Activity Experience, and Sex Differences on Tests of Mental Rotation Ability. *Laterality*, **7**, 59-74. https://doi.org/10.1080/13576500143000078

[45] Witelson, S.F. (1976) Sex and the Single Hemisphere: Specialization of the Right Hemisphere for Spatial Processing. *Science*, **193**, 425-427. https://doi.org/10.1126/science.935879

[46] Randles, R.H. and Wolfe, D.A. (1979) Introduction to the Theory of Nonparametric Statistics. Wiley, New York.

[47] Christova, P.S., Lewis, S.M., Tagaris, G.A., Uğurbil, K. and Georgopoulos, A.P. (2008) A Voxel-by-Voxel Parametric fMRI Study of Motor Mental Rotation: Hemispheric Specialization and Gender Differences in Neural Processing Efficiency. *Experimental Brain Research*, **189**, 79-90. https://doi.org/10.1007/s00221-008-1405-x

[48] Lee, N., Choi, H. and Kim, S.H. (2016) Bayes Shrinkage Estimation for High-Dimensional VAR Models with Scale Mixture of Normal Distributions for Noise. *Computational Statistics & Data Analysis*, **101**, 250-276. https://doi.org/10.1016/j.csda.2016.03.007

[49] Ingalhalikar, M., Smith, A., Parker, D., Satterthwaite, T.D., Elliott, M.A., Ruparel, K., Hakonarson, H., Gur, R.E., Gur, R.C. and Verma, R. (2014) Sex Differences in the Structural Connectome of the Human Brain. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, 823-828. https://doi.org/10.1073/pnas.1316909110

What is SCIRP?

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

What is Open Access?

All original research papers published by SCIRP are made freely and permanently accessible online immediately upon publication. To be able to provide open access journals, SCIRP defrays operation costs from authors and subscription charges only for its printed version. Open access publishing allows an immediate, worldwide, barrier-free, open access to the full text of research papers, which is in the best interests of the scientific community.

- High visibility for maximum global exposure with open access publishing model
- Rigorous peer review of research papers
- Prompt faster publication with less cost
- Guaranteed targeted, multidisciplinary audience

Scientific
Research
Publishing

Website: https://www.scirp.org

Subscription: sub@scirp.org

Advertisement: service@scirp.org