

Investigation of Brain Regions Responsible for The Processing of The Stimulus Novelty by Using Functional Magnetic Resonance Imaging

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ABSTRACT

Introduction: Novelty processing is one of the basic survival mechanisms for living organisms. Among the various types of novelty, stimulus novelty is the effect created by stimuli that are unlikely to be encountered throughout one's lifetime. However, the oddball design mostly used in studying stimulus novelty also includes an obligatory contextual novelty effect, which actually requires the presence of schemas about sensory input in the memory. In this study, we aimed to investigate the neural circuits related purely to the detection of stimulus novelty using functional magnetic resonance imaging (fMRI) by applying an experimental design that excludes any contextual novelty effect.

Methods: Fifteen right-handed healthy participants were included in the study. The stimulus novelty effect was generated by the images of object-like structures that could not be named and did not correspond to a real object. These stimuli were shuffled with images of familiar objects frequently encountered in daily life. SPM12 and CONN were used for the preprocessing stages and activation analysis of fMRI data. In the

analyses, the cluster formation threshold was determined as $p < 0.001$ and the cluster level significance threshold with family-wise error (FWE) correction was set at $pFWE < 0.05$.

Results: The activity of the fusiform, middle occipital, inferior occipital and superior occipital gyri increased during the processing of the stimulus novelty, while the activity of the inferior parietal cortex and supramarginal gyrus decreased.

Conclusion: With the experimental paradigm that excluded the confounding effects of contextual novelty, anatomical regions that respond specifically to stimulus novelty could be identified. Our results suggest that, while stimulus novelty intensively activates brain areas related with higher-order visual processing, the brain regions that associate sensory inputs with the schemas in the memory are less active.

Keywords: Functional magnetic resonance imaging, novelty processing, stimulus novelty, visual processing

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INTRODUCTION

The processing of novelty is mainly based on comparing the individual's current predictions and the sensory input. As a result of this comparison, if the inputs do not match the individual's current predictions, they are considered novel (1). Updating existing schemas as a result of comparing novel inputs with existing information forms the basis of one of the important survival mechanisms.

While different types of novelty have been described in the literature, the two most basic types of novelty are the contextual novelty and the stimulus novelty. Contextual novelty is the effect created by stimuli incompatible with a particular context, while stimulus novelty is defined as the effect created by stimuli that are unlikely to be encountered throughout life and therefore do not have any representation in the memory (2). During processing of stimulus novelty, the brain is confronted with sensory inputs that have no categoric representation

Highlights

- Brain responses to stimulus novelty were examined using fMRI.
- Stimulus novelty is processed predominantly in higher-level visual areas.
- Novel stimuli are less associated with memory schemas.

or schema in the memory, in contrast to the contextual novelty which is based on the incompatibility of the sensory input with the current expectation or prediction created by the specific sensory context.

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Therefore, in-depth analysis of the stimulus novelty, during which the brain encounters the image of a pseudo-object that does not exist in the world, can shed light on the importance of the memory schemas in general novelty processing.

Although the processes related to the detection and processing of contextual novelty have been investigated widely, only limited number of studies on the stimulus novelty are present in the current literature. It has been reported that the novelty processing, which is usually examined through the visual sense, leads to activation of common anatomical areas, including the hippocampus, parahippocampal cortex (PHC), entorhinal cortex, perirhinal cortex, fusiform gyrus (FG), inferior occipital gyrus (IOG) and middle occipital gyrus (MOG), regardless of the type of novelty (1,3,4). However, the experimental designs used in these studies are not suitable for clearly distinguishing the effects of contextual novelty and stimulus novelty.

Research on novelty processing began in the 1970 s by modifying the conventional oddball experiment, which is a target detection task (5). In the classical oddball design, constant and task-relevant target stimuli, are randomly interspersed with a low-probability among a series of constant and frequent standard stimuli. For the so-called novelty paradigm, the oddball paradigm is modified by introducing, task-irrelevant stimuli of familiar items, which have a low-probability similar to that of the targets but are never repeating themselves along the experiment in order to generate the novelty effect. In this way, the novelty effect created by the task-irrelevant stimuli deviating from the target detection context of the oddball task resulted in the early years into significant event-related potential (ERP) wave components in the electroencephalogram (EEG), which later on could also be investigated in terms of their generation sites by using fMRI (6–8). The few studies addressing stimulus novelty yet have used unrecognizable sensory inputs in this experimental design. However, these inputs containing stimulus novelty also contain a contextual novelty effect due to their deviation from the high-probable standard stimuli that constitute the context of the task (7,8). Therefore, with this oddball-like design, stimulus novel stimuli inevitably also contained the effect of deviating from the task context. Consequently, we argue that it is not possible to separate the pure effects of contextual novelty and stimulus novelty within the data of these experiments.

The main aim of the present study is to focus purely on the brain areas that are responsible for the processing of stimulus novelty by using an appropriate experimental design in order to exclude the confounding contextual novelty effect generated in the oddball-like novelty experiments. In this way, we aim to observe purely the effects of stimulus novelty, that corresponds to stimuli that do not have a memory trace. Within this context, the term “novel” in the present study will correspond to stimulus novelty, while the term “non-novel” will be used to indicate absence of the stimulus novelty effect. The data was evaluated with a whole-brain, voxelwise fMRI analysis in order to explore the overall properties of the neural circuits involved in the processing of stimulus novelty.

METHODS

Participants

Fifteen right-handed healthy participants (5 females, 10 males; mean age=27.2±4.2 years, range=21–35 years; mean education=16.4±3.1 years, range=12–23 years) without any neurological or psychiatric diagnosis participated in the study. First, Beck Depression and Beck Anxiety Scales were administered to the participants, and those showing symptoms of depression and anxiety were excluded from the study (9–12).

Additionally, the Addenbrook Cognitive Assessment Battery was used to evaluate the general cognitive status of the participants (Mean=96.8±3.5, range=89–100) (13). The study design was approved by the İstanbul Üniversitesi İstanbul Tıp Fakültesi Klinik Araştırmaları Ethics Committee to be ethically appropriate (22/04/2022-08).

Experimental paradigm

The experimental paradigm used in the study was prepared using E-prime (Version 2.0, Psychology Software Tools) software. To investigate the processing of stimulus novelty, images of pseudo-object were used, which, although having a 3-dimensional object view, cannot be named and do not correspond to any real object. The novel objects used in the study were obtained from the The Novel Object and Unusual Name (NOUN) database (14). In order to exclude the contextual novelty effect caused by the oddball design widely used in novelty studies, the task of detecting target stimuli interspersed among frequent standard stimuli was not used in the present study. Furthermore, the stimulus novel pseudo-object images were presented among familiar stimuli that did not belong to a specific category (equal number of objects belonging to equipment, garden, clothing, electronics, furniture, stationery, music, vehicle, sports and other categories), in order to avoid also any contextual effect that might be produced by a specific category of familiar items (15). To further avoid also any familiarity effect for a specific item, items of both stimulus types did not repeat, hence were always changing throughout the experiment. Thus, the contrast between the two stimulus types was ensured to represent pure stimulus novelty. From this point on the term “novel” will be used for the stimulus novelty, while the term “non-novel” will correspond to stimulus non-novelty.

In order to maintain the participants' attention during the experiment, they were asked to evaluate whether the stimuli they saw were bigger or smaller than a shoebox and respond using the buttons in their right hands. The experiment was repeated in 3 blocks, and the blocks were randomly presented to the participants using the Latin square method. While 20 of the stimuli in each block contained the stimulus novelty effect, 60 stimuli consisted of familiar stimuli. The 240 visual stimuli used in the experiment were standardized and converted to 500×500 pixel size. The experimental paradigm used in the study is presented in Fig. 1. Data analysis were performed on the whole data set by combining the 3 blocks.

The experimental paradigm was created using event-related design (16). The visual stimuli used in the experiment were presented in color on a white screen for 2000 ms, and a “+” shaped fixation point was presented in the center of the screen at varying intervals for the inter-stimulus intervals. In order to distinguish hemodynamic responses to stimuli presented at short intervals, the order of stimulus types and inter-stimulus intervals (500 to 5000 ms) were optimized using optseq software (<http://surfer.nmr.mgh.harvard.edu/optseq/>) (17).

MRI acquisition

Anatomical and functional MRI images were obtained using a 3 Tesla MRI device (Phillips, Achieva, Best, The Netherlands) and a 32-channel head coil at İstanbul Üniversitesi Hulusi Behçet Yaşam Bilimleri Araştırma Laboratuvarı (HUBAL). Anatomical MRI data were recorded with a high-resolution T1-weighted 3D Turbo Field Echo (TFE) sequence with the following parameters: time of repetition (TR): 8.1 ms, time of echo (TE): 3.7 ms, flip angle: 7°, field of view (FOV): 256×256 mm, voxel size: 1 mm³ (isotropic) and 176 sagittal slices and total scan time: 6 minutes 11 seconds. Functional MRI data were obtained with a T2* weighted gradient-echo echo-planar imaging (EPI) sequence using the following parameters: voxel size: 2×2×4, TR: 2000 ms, TE: 30 ms, flip angle: 77°,

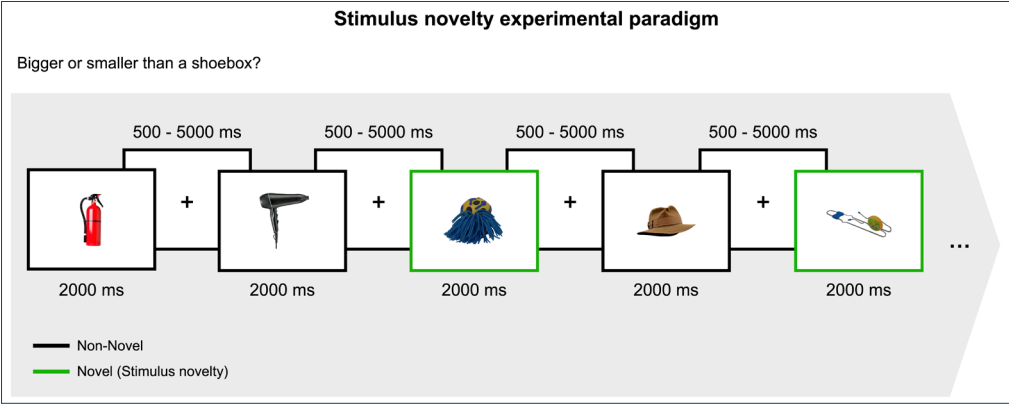


Figure 1. In the experimental paradigm, the stimulus novelty effect was isolated by presenting images of novel (stimulus novel) vs familiar, non-novel (stimulus non-novel) objects from various categories. Stimuli were presented on the screen for 2000 ms, and the inter-stimulus interval (ISI) varied between 500 and 5000 ms.

FOV: 224×240 mm and 36 axial slices (anterior commissure-posterior commissure aligned) and total scan time: 12 minutes.

Neuroimaging Data Analysis

Standard preprocessing steps were applied to purify functional data from movement-related artifacts and reduce the effect of individual differences. CONN 22a (Functional connectivity toolbox, <https://web.conn-toolbox.org/home>) and SPM12 (Statistical Parametric Mapping, <https://www.fil.ion.ucl.ac.uk/spm>) software running in MATLAB environment were used for the preprocessing steps (18,19).

First, a realignment was performed to eliminate motion-related artifacts that may occur during fMRI recording, and the images were realigned and 3 rotation and 3 translation values were obtained to be used in further analysis. For outlier detection, motion and global signal changes were detected by comparing consecutive images with Artifact Detection Tools (ART). Images with movement-related deviations of over 0.9 mm or global blood oxygenation level-dependent signal changes of over 5 standard deviations were considered outlier images (20). Sessions in which the number of participants’ outlier images exceeded 10% of the total number of images in the session were excluded from the analysis. In the next stage, functional images with low spatial resolution were co-registered with high-resolution anatomical images. They were segmented into white matter, gray matter and cerebrospinal fluid compartments using anatomical images as a reference (21,22). T1-weighted anatomical images and co-registered functional data were normalized to 2 mm isotropic voxels when transferred to the MNI 152 template (23). Finally, the functional data were smoothed by spatial convolution with an isotropic Gaussian kernel (full-width half maximum=6 mm).

General linear model (GLM) analysis was performed using SPM12 to detect stimulus novelty-related brain activations. In addition to the

stimuli modeled in the design matrix, 6 movement parameters and outlier images obtained during the realignment step were defined as regressors to exclude movement-related effects in GLM. A high-pass filter with a cutoff at 128 seconds was applied to clean the slow oscillations. As a result of first-level analyses, *b* regression coefficients reflecting the relationships of experimental conditions with activation in each voxel were calculated. In statistical comparisons, activation changes in the *novel > non-novel* and *novel < non-novel* contrasts were examined using paired samples t-test. In the analyses, the cluster-forming threshold was determined as *p* <0.001, and the significance threshold at the cluster level was determined as *p* <0.05 after FWE correction. Automated Anatomical Labeling (AAL) atlas was used to identify anatomical regions where significant differences were detected (24).

RESULTS

Functional Neuroimaging results

fMRI activation analyses revealed two clusters (Cluster 1: *t*=7.14, *p* <0.001; Cluster 2: *t*=5.56, *p*=0.001) that increased activation during the perception of the stimulus novel compared to stimulus non-novel stimuli were detected, while three clusters (Cluster 1:*t*=5.94, *p* <0.001; Cluster 2: *t*=5.06, *p*=0.001; Cluster 3: *t*=5.01, *p* <0.001) displayed significantly decreased activity. Clusters showing increased activity during processing of the stimulus novelty included the right fusiform gyrus (FG), right superior occipital gyrus (SOG), and bilateral middle (MOG) and inferior (IOG) occipital gyri, while three clusters including the right supramarginal gyrus (SMG) and bilateral inferior parietal cortices (IPC), calcarine cortices and lingual gyri (LG) displayed stronger activity during the processing of the stimulus non-novel inputs. Detailed information about activations is shown in Table 1 and Fig. 2.

Table 1. Activation analysis results of the stimulus novelty effect

Cluster	Anatomical region	MNI Coordinate			Voxel number	t value	p value	Cohen's d
		x	y	z				
Novel > Non-novel								
1	Right hemisphere: IOG, MOG, FG, SOG	+34	-88	-04	2259	7.14	<0.001	0.723
2	Left hemisphere: IOG, MOG	-28	-94	-08	299	5.56	0.001	0.568
Novel < Non-novel								
1	Right hemisphere: SMG, IPC	+46	-38	+38	453	5.94	<0.001	-0.986
2	Bilateral hemisphere: calcarine cortex, LG	+10	-80	+04	293	5.06	0.001	-0.727
3	Left hemisphere: IPC	-52	-46	+46	527	5.01	<0.001	-1.082

IPC: Inferior parietal cortex; MOG: Middle occipital gyrus; IOG: Inferior occipital gyrus; SOG: Superior occipital gyrus; LG: Lingual gyrus; FG: Fusiform gyrus; SMG: Supramarginal gyrus. Comparisons were made using paired sample t-test. The cluster forming threshold of *p* <0.001 and cluster-level *p*_{FWE} <0.05 were considered as the significance threshold.

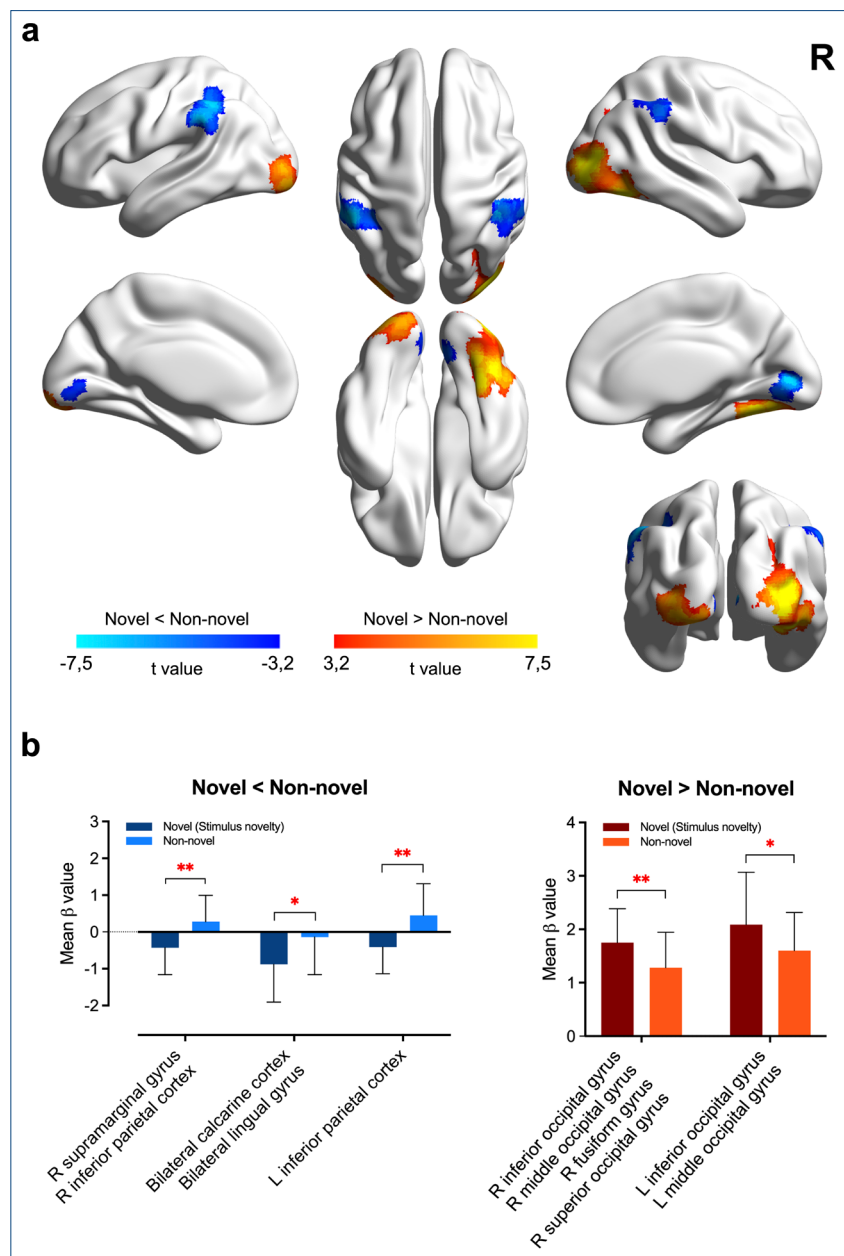


Figure 2. a, b. Results of the stimulus novelty activation analyses. Anatomical regions that show activation changes during novel stimuli compared to non-novel stimuli are presented (a). Average b values for the clusters of the novel < non-novel (left) and novel > non-novel (right) contrast are shown (b). *pFWE < 0.05; **pFWE < 0.01.

DISCUSSION

In this study, the anatomical regions involved in the processing of stimulus novelty were investigated using the fMRI method by specifically focusing on the experimental design in order to exclude confounding effects of contextual novelty. As a result of the study, activation in IOG, MOG, SOG and FG increased during stimulus novelty, while SMG and IPC, LG and calcarine cortex showed a significant activation decrease in comparison with the processing of the stimulus non-novel items. In neuroimaging studies investigating stimulus novelty, a widespread activation pattern involving frontal areas and MTL structures, predominantly occipital areas, has been reported (4,6,8,25,26). In an fMRI study using an oddball-like novelty experiment, Mandelbrot fractal images were used to generate the stimulus novelty effect as they represent a set of structured images not usually encountered in daily life. As a result of the study, it was reported that the activity of bilateral FG, PHC, hippocampus and left SMG increased during novel stimuli compared to standard stimuli (25). In another fMRI study using similar stimuli, increased activation was reported in anatomical areas including MOG, LG, FG, PHC, inferior

temporal gyrus, cuneus, precuneus and inferior frontal gyrus (IFG) during novel stimuli (8). In an fMRI study, in which parts of different objects were combined to create a stimulus novelty effect by producing objects that have no equivalent in real life, they were compared with familiar objects. A significant increase in activity was reported in the LG, MOG and precuneus during the processing of the synthesized objects (26). However, since the majority of these studies used the oddball experimental design and novel stimuli deviated from the task context created by standard and target stimuli, they also include a contextual novelty component in addition to stimulus novelty.

In our study, MOG, IOG, SOG and FG, which showed increased activation during processing of the stimulus novelty, were associated with object recognition and visual perception (4,27). These anatomical regions, which show a consistent increase in activation during stimulus novelty, are located in the lateral occipital cortex, which is known to play an important role in object recognition processes (28,29). It has also been suggested that MOG contributes to the process of comparing new object

representations with existing object representations (30). Our findings indicate that these anatomical regions subserving visual perception show a more intensive use of resources for the identification of novel stimuli which are not represented in the memory or cannot be incorporated into any schema. On the other hand, the decrease in activation in the LG and calcarine cortex during stimulus novelty compared with the processing of familiar objects can be interpreted within the framework of the functions attributed to these anatomical regions in terms of holistic shape decoding and visual memory. Both functions seem to play a role in comparing and associating the present visual input with the existing schemas in the memory. On the other hand, the study in which parts of different familiar objects were combined to create a stimulus novelty effect reported a significant increase in the LG activity (26). This finding, which in the first line seems to oppose our results on stimulus novelty, suggests that LG has the capacity to process the components of a visual input containing defined formal elements, even if the input, as a whole, does not correspond to a known object. Our results extend this interpretation by showing that the LG's role in object recognition decreases significantly as the definition of even parts of a visual input can be associated with any existing schema.

Additionally, the activation decreases in IPC and SMG during processing of the stimulus novelty in the present study are generally in accordance with the functions assigned to these areas. In the literature, IPC has been associated with many different functions, such as maintaining attention, interpreting sensory input, language and novelty processes (31,32). Numssen et al. (2021) aimed to investigate the language functions of IPC by using meaningful and meaningless words in their fMRI study. This study reported that IPC increased its activation during the processing of meaningful words compared to meaningless words (32). In addition, it has been reported that parietal areas, especially IPC and angular gyrus, play important roles in interacting with memory and associating stimuli with the schemas existing in the memory (33). On the other hand, in a study by Downar et al. (2002) in which the effects of contextual novelty were investigated using stimuli deviating from a frequent standard stimulus, SMG has been suggested to play a role in identifying out-of-context stimuli (34). In this context, the decrease in activation in parietal areas during stimulus novelty can be explained by the inability to associate the visual inputs with schemas in memory.

Although increased activation in the IFG was consistently reported in the literature in novelty studies using oddball-like designs, no change in activation in the IFG was detected in our study (6,8,35). It has been reported in various studies that the IFG plays a role in evaluating the relationship of stimuli to the task and in preventing impulsive responses to stimuli that do not require a response (34,36,37). In this context, our findings support the fact that IFG is a structure involved in response inhibition processes rather than the novelty detection. As a result, the novelty paradigm used in the present study seems to greatly reduce or exclude confounding effects by also inhibiting the response to rare but task-irrelevant novel stimuli that occur in novelty experiments derived from the oddball paradigm.

Although the experimental paradigm used in our study and the analysis methods for neuroimaging data were meticulously designed in detail, there is still a limitation due to the rather limited number of participants. To handle this problem, we tried to increase the reliability of statistical analyzes by applying conservative statistical corrections.

CONCLUSION

Although novelty processing as an important component of survival is widely investigated in the literature, experimental paradigms to investigate its different subtypes and their specific effects are not well structured yet. The stimulus novelty, which corresponds to an absolute novelty of the sensory input in terms of the absence of any associated

schema in memory, should require significantly different processes compared with other types of novelty processing, for which the stimulus may be a well-defined but out-of-context item. The present study, by designing an experimental paradigm that excludes confounding effects of contextual novelty, focused on the anatomical regions that respond specifically to stimulus novelty. Our results revealed, in contrast to the widely distributed brain areas reported in association with stimulus novelty, that specifically higher-order visual areas such as FG, MOG, IOG and SOG are active as the brain is confronted with an absolutely novel stimulus, while other widely reported areas such as IPC or SMG were less active compared with the processing of the familiar objects, which even when presented in a contextually novel situation are first associated with existing memory representations in order to evaluate the contextual novelty effect. As a result, we propose that a careful analysis of the different types of novelty processing, especially in terms of the presence or absence of the possibility to compare or associate the sensory input with an existing schema or memory representation may shed light on the neural underpinnings of such an important cognitive faculty.

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Ethics Committee Approval: The study was approved by the Ethics Committee of Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 22/04/2022 / Decision No: 08).

Informed Consent: Consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- EH, TD; Design- EH, TD; Supervision- EH, TD; Data Collection and/or Processing- EH; Analysis and/or Interpretation- EH, TD; Literature Search- EH, TD; Writing- EH; Critical Reviews- TD.

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