



**HAL**  
open science

## **An Echo of Consciousness: Brain Function During Preferred Music**

Manon Carrière, Stephen Karl Larroque, Charlotte Martial, Mohamed Ali Bahri, Charlène Aubinet, Fabien Perrin, Steven Laureys, Lizette Heine

► **To cite this version:**

Manon Carrière, Stephen Karl Larroque, Charlotte Martial, Mohamed Ali Bahri, Charlène Aubinet, et al.. An Echo of Consciousness: Brain Function During Preferred Music. *Brain connectivity*, 2020, 10 (7), pp.385-395. 10.1089/brain.2020.0744 . hal-04692146

**HAL Id: hal-04692146**

**<https://hal.science/hal-04692146v1>**

Submitted on 9 Sep 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# An Echo of Consciousness: Brain function during preferred music

Running head: Brain function during preferred music in DOC

Manon Carrière<sup>1,2</sup> MSc, Stephen Karl Larroque<sup>1,2</sup> MSc, Charlotte Martial<sup>1,2</sup> PhD, Mohamed Ali Bahri<sup>3</sup> PhD, Charlène Aubinet<sup>1,2</sup> MSc, Fabien Perrin<sup>4</sup> PhD, Steven Laureys<sup>1,2\*</sup>, MD PhD, Lizette Heine<sup>4</sup> PhD\*

<sup>1</sup> Coma Science Group, GIGA-Consciousness, University and University Hospital of Liège, Liège, Belgium.

<sup>2</sup> Centre du Cerveau<sup>2</sup>, University Hospital of Liège, Liège, Belgium

<sup>3</sup> GIGA-Cyclotron Research Center In Vivo Imaging, University of Liège, Belgium

<sup>4</sup> Centre de Recherche en Neurosciences de Lyon, Inserm U1028 - CNRS UMR5292, University of Lyon 1, Bron, France

\* – Both authors share the last position.

## Correspondence:

Name: Steven Laureys

Mailing address: steven.laureys@uliege.be

Address:

Coma Science Group, GIGA-Consciousness, University of Liège

Centre du Cerveau<sup>2</sup>, University Hospital of Liège

Avenue de l'hôpital 1

4000 Liège

Belgium

## **Keywords:**

MRI - Disorders of consciousness – Music – Functional connectivity – (Fractional)

Amplitude of Low Frequency Fluctuation

## ABSTRACT

### Background

Given its emotional and autobiographical properties, music appears as a potential aid in diagnostic assessment and therapeutics in patients with disorders of consciousness (DOC). Several studies have shown boosting effects on behavior and brain functioning when patients were exposed to (their preferred) music.

### Objective

To investigate if these effects on the brain's spontaneous activity are dependent on the level of consciousness.

### Methods

Nine post-comatose patients and eight healthy control subjects were assessed using fMRI in two conditions: rest (without stimulation) and music. All patients presented at least an auditory startle, thereby suggesting the presence of residual auditory function. A gradient of consciousness (from unresponsive wakefulness syndrome to healthy subjects) was formulated to evaluate consciousness-level-dependent increases in brain activity and connectivity. Network-based functional connectivity assessed auditory, default-mode, frontoparietal and music-evoked emotions networks. Furthermore, exploratory voxel-to-voxel analyses were performed at the whole brain level using intrinsic connectivity contrast and (fractional) amplitude of low frequency fluctuations.

### Results

Stronger consciousness-level-dependent increases within network-to-voxel analysis of connectivity were found in the frontoparietal network with the precuneus during music stimulation compared to rest. Voxel-to-voxel analyses showed stronger increases of intrinsic connectivity in the music condition compared to rest in regions previously related to music processing. There were consistently more regions with increased connectivity during the main effect of music compared to rest. These increases of connectivity during

music were observed in brain regions involved in consciousness, language, emotion and memory processing.

## Conclusions

Our results show that music seems to trigger more substantial connectivity changes compared to rest, pointing towards the potential ability of music to stimulate patients' brain function. Further research should focus on effects of music in general, its specific acoustical features and the effects of simple auditory stimuli, as well as the possible therapeutic and diagnostic effects of music in well controlled clinical trials.

## Impact Statement

Due to its emotional and autobiographical properties, music is a particularly salient stimulus. A few studies using musical stimuli have shown promising results in terms of behavioral responsiveness in patients with DOC (Magee, 2005; Raglio *et al.*, 2014; Verger *et al.*, 2014). Our study confirms the presence of a beneficial effect of music on brain connectivity in these severely brain-injured patients, which moreover seems to be dependent of the level of consciousness. Our findings therefore strengthen the hypothesis that music could play a role from a diagnostic and therapeutic standpoint in this population, paving the way for future well-controlled clinical trials.

## 1. Introduction

Disorders of consciousness (DOC) remain a very challenging pathological condition. After emerging from coma, severely brain-injured patients may pass through several altered states of consciousness. In the unresponsive wakefulness syndrome (UWS - The Multi-Society Task Force on PVS, 1994), patients are awake but show no signs of awareness of themselves or their environment. Once they demonstrate unequivocal (but often inconsistent) behavioral evidence of self or environmental awareness, they are said to be in a minimally conscious state (MCS - Giacino *et al.*, 2002). Some patients present a cognitive motor dissociation, demonstrating consciousness using novel neuroimaging techniques while being unresponsive at the bedside (Schiff, 2015). Patients emerge from MCS (EMCS) when they regain functional communication or objects use (Giacino *et al.*, 2002). Besides, patients suffering from locked-in-syndrome (LIS) are frequently mistakenly diagnosed as unconscious due to motor paralysis which prevents them from expressing their consciousness and cognitive abilities (Schnakers *et al.*, 2008). The ability to manifest consciousness is indeed jeopardized by such limited motor responses, but also by significant cognitive and sensory impairments, as well as vigilance fluctuations (Schnakers *et al.*, 2009). Consciousness is thus difficult to assess in these non-communicative patients, and repeated assessments by trained clinicians are needed (Wannez *et al.*, 2017a) to provide a reliable and accurate diagnosis, which crucially influences important medical and therapeutic decisions (Boly *et al.*, 2008; Demertzi *et al.*, 2011).

There is some indication that the use of salient or autobiographical stimuli could optimize arousal and allow more accurate diagnoses (Perrin *et al.*, 2015). DOC patients would indeed be more responsive when assessed with personally salient versus neutral stimuli. Improved scores on the most sensitive standardized behavioral assessment scales (Coma Recovery Scale-Revised; CRS-R - Giacino *et al.*, 2004) can be seen with, for example, self-related objects to evaluate functional use of objects (Sun *et al.*, 2018), a mirror to assess visual pursuit (Wannez *et al.*, 2017b) and the own name to evaluate localization to sound (Cheng *et al.*, 2013). Music has specifically received special attention in recent literature (for a review, see Grimm and Kreutz, 2018), as music can be very personal. For example, higher CRS-R scores and more frequent spontaneous signs of consciousness are observed after

preferred music exposure (Verger *et al.*, 2014). Using electroencephalography, exposure to preferred music increases the probability to observe a P300 response to one's own name in DOC patients (Castro *et al.*, 2015). Authors hypothesize that this is due to its emotional and self-related properties. Furthermore, several case studies have so far reported potential long-term effects of music therapy on behavioral responses (e.g., increased eye contacts and smiles, reduction of annoyance, inertia or psychomotor agitation) (Magee, 2005b; Raglio *et al.*, 2014)

The search for more reliable diagnoses often uses neuroimaging to assess residual brain function. Resting-state functional MRI (fMRI) is one such tool and allows for the exploration of several reproducible brain networks without the need for patients' cooperation. In DOC, this technique has proven to be a valuable tool to complement the behavioral assessment as it shows a decrease in functional connectivity (Heine *et al.*, 2012) and can distinguish between UWS and MCS patients (Demertzi *et al.*, 2015). Such a linear relation between functional connectivity and consciousness in resting state networks can be extended to EMCS patients (Di Perri *et al.*, 2016). Notably, the auditory network has been shown with the strongest power to distinguish between UWS and MCS, allowing for automatic classification (Demertzi *et al.*, 2015).

The first fMRI study on music in DOC found an activation in auditory regions for healthy control subjects (HCS) and MCS patients, as well as in one UWS patient who would soon evolve into MCS (Okumura *et al.*, 2014). Another study showed that within patients, changes in functional connectivity might be related to the auditory network implied in rhythm and music perception, and to cerebral regions within the frontoparietal network linked to autobiographical memory (Heine *et al.*, 2015). The findings that music 'boosts' cognitive functions leads to the hypotheses that salient sensory stimuli might temporarily bring the patients' brain function to its full potential, which can thus improve diagnostic assessment.

Within the present study we aim to assess if these observed effects of music on the brains' spontaneous activity are dependent on the level of consciousness. To do so we formulated a gradient of consciousness (from UWS to HCS) and we explored functional connectivity (with a priori network-based analysis and exploratory voxel-to-voxel analysis) and spontaneous regional brain activity ((fractional) Amplitude of Low Frequency Fluctuation -

fALFF) changes during a music and a rest condition. We expect to observe a stronger linear correlation with the level of consciousness during music.

## 2. Materials and methods

### 2.1. Participants

Eight HCS (four females; mean age = 26 years,  $SD = 3$ ; Table 1) and twelve patients (4 UWS, 2 MCS, 3 EMCS, 3 LIS) were included in the study between March 2014 and April 2018. All the HCS and five of the twelve patients were the same as in a previous study (Heine *et al.*, 2015). Inclusion criteria for HCS were the absence of history of neurological or psychiatric disorders. Inclusion criteria for patients were: 1) prolonged DOC or LIS (>1month post-injury), 2) absence of contraindications for MRI (e.g., presence of ferromagnetic aneurysm clips, pacemakers), 3) absence of sedation in the scanner, 4) absence of extensive brain damage making the analyses impossible (i.e., more than 2/3 of one hemisphere), 5) multiple behavioral assessments using the CRS-R performed by experienced clinicians (except for LIS patients), including one on the same day prior to the MRI acquisition. The study was approved by the ethics committee of the medical school of the University of Liège.

[TABLE 1]

### 2.2. Protocol and data acquisition

The protocol and data acquisition were performed as previously described (Heine *et al.*, 2015). Five excerpts of preferred musical pieces were selected from a questionnaire completed by the participants themselves (for the HCS) and by the loved ones (for the patients), and combined to create a musical stimulus over the duration of the functional MRI sequence. A 3T tesla (Siemens Magnetom TrioTim) was used at the University Hospital Center of Liège. A high-resolution T1-weighted image was acquired, as well as T2\*-weighted fMRI images (300 volumes, 32 slices, voxel size =  $3.0 \times 3.0 \times 3.75 \text{ mm}^3$ , repetition time = 2000 ms, echo time = 30 ms, flip angle =  $90^\circ$ , field of view = 384 mm, matrix size (I, J, K) =  $64 \times 64 \times 32$ , delay = 0, slice order = sequential descending, Echo Planar Imaging sequence with axial slice orientation). Two functional scans were acquired during one MRI scanning session: one with the participants' preferred music (i.e., music condition) and one

when participants were exposed only to the noise of the scanner (i.e., rest condition). These two functional scans were always separated by a period of 10min to reduce any potential order effects, and the order of the conditions was randomized between participants. We delivered instructions and music through MR compatible Siemens headphones. Both HCS and patients were asked to keep their eyes closed and not think of anything in particular (compliance of patients cannot be guaranteed due to their condition).

### 3. Data pre-processing

#### 3.1. Structural imaging

Structural (T1\*-weighted) MRI images were manually reoriented to the anterior commissure/posterior commissure (AC-PC) scheme and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and normalized into the MNI space, using the old segmentation module and standard tissue probability map of Statistical Parametric Mapping 12 (SPM12) ('Statistical Parametric Mapping 12', n.d.) under MATLAB R2011A.

#### 3.2. Resting-state fMRI

Functional volumes were manually reoriented into the corresponding structural images, and then preprocessed by using SPM12. First, the EPI volumes were corrected for the temporal difference in acquisition among different slices using the slice timing correction module with the reference slice set to the first temporal slice, and then the images were realigned to the first volume for head-motion correction. The mean BOLD image across all realigned volumes was then coregistered with the structural image. The normalization transformation from subject space to MNI space was then applied to the coregistered BOLD images, hence applying an indirect normalization. Finally, all the coregistered BOLD images were smoothed (8 mm full-width half-maximum). To reduce loss of data or subject exclusion due to motion artifacts, we used the artifact detection toolbox (NITRC ART) for artifact detection and rejection using a composite motion measure (largest voxel movement) with a "liberal" threshold (global threshold 9.0, motion threshold 2.0, use scan-to-scan motion and global signal). With this approach, a volume was defined as an



outlier (artifact) if the largest voxel movement detected was above the specified thresholds. We subsequently included outliers in the global mean signal intensity and motion as nuisance regressors (i.e., one regressor per outlier in the first-level general linear model). Thus, the temporal structure of the data was not disrupted. Several parameters were included in a linear regression using CONN v17F (Whitfield-Gabrieli and Nieto-Castanon, 2012) and SPM12 to remove possible spurious variances from the data. These were i) six head motion parameters obtained in the realigning step, along with their 1<sup>st</sup>-order derivatives, ii) the scrubbed BOLD volumes with too much motion as detected with the ART toolbox's composite motion measurement with a liberal setting, iii) non-neuronal noise signal derived by the anatomical component-based noise correction method (aCompCor - Behzadi *et al.*, 2007), which defines noise signal as the top five principal components from subject-specific white matter and the top five from cerebral spinal fluid, iv) the effect of each session's start to reduce the impact of MRI magnetization oversaturation, v) a linear detrending to the overall resulting BOLD signal. Then the residual time series were linearly detrended (no despiking) and temporally band-pass filtered (0.008-0.09 Hz) using CONN's denoising procedure.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## 4. Statistical analysis

### 4.1. Resting-state fMRI

We conducted the analysis of the fMRI resting state functional connectivity via the CONN v17F toolbox under MATLAB R2017A by using two types of analysis: i) a seed-based correlation analysis (SCA) approach, more specifically network-to-voxel to cover changes in correlation of the BOLD signal in the whole brain with respect to the specified seed regions; and ii) voxel-to-voxel connectivity measures without a priori seeds, in order to analyze globally the brain connectivity patterns.

Both for seed-based and exploratory voxel-to-voxel analyses, 2<sup>nd</sup>-level statistical analyses were performed in order to make between-groups and between-conditions comparisons. Regarding the between-groups comparison, we created a contrast that assumes a linear

correlation between the state of consciousness and the connectivity's z-values: [-3 -1 1 3] for respectively the UWS, MCS and EMCS, LIS and HCS (with the MCS and EMCS patients merged in one single group). This contrast was specifically designed to produce a linear regression with a constant slope of 2 between our four groups. Regarding the between-conditions comparison, three different contrasts were used: main effect of the rest condition ([1 0]), main effect of the music condition ([0 1]), and a paired t-test difference between both conditions to highlight the effect of music compared to rest ([-1 1], or music > rest). In short, a significant positive correlation with the level of consciousness in music > rest means that conscious subjects display increases in positive correlations compared to less conscious states that are more marked during music than rest.

We showed brain connectivity if the main effect contrast (i.e., under a single condition) or the difference in correlation between conditions effect size allows to disambiguate the conditions.

#### **4.1.1. Network-to-voxel analysis**

Using CONN, we used extracts from fMRI BOLD time series from a region of interest (the seed) and measured the temporal correlation between this signal and the time series of all other brain voxels. This process was repeated for each subject and each region of interest. We investigated the following networks, as composed of a set of regions of interests using an average effect contrast (i.e., uniformly weighted contrast, equivalent as to having one region of interest covering the entire network): the default-mode (DMN) and the fronto-parietal (FPN) networks, derived from the Harvard-Oxford atlas provided by CONN. We also assessed the auditory network using a 10mm radius sphere around coordinates as defined in previous studies (Demertzi *et al.*, 2015). Furthermore, using the coordinates provided by a meta-analysis of 21 previous studies, we explored a 'music-evoked emotions' network using a 5mm radius sphere around coordinates (Koelsch, 2014). The regions of interest composing each network and their coordinates are detailed in Suppl. Mat. V.

#### 4.1.2. Exploratory voxel-to-voxel analyses

We examined the global brain connectivity patterns, without any a priori seed, between each voxel and the rest of the brain using two measures. First, the Intrinsic Connectivity Contrast (ICC; in CONN toolbox) which permits to observe “the sum of the correlation of each source voxels to every other voxel in the brain, which is then weighted by the root mean square of the correlation coefficient values associated with the voxel-to-voxel connection”. Second, the ALFF and fractional ALFF (fALFF; present in the CONN toolbox), which are not connectivity measures per se, but thought to reflect cortical excitability and long-range neural synchronization of spontaneous neuronal activity. They can be seen as measures of the variation in the amplitude of the BOLD signal, by calculating the power in the very low frequencies, usually 0.01–0.08 Hz, hence complementing connectivity analyses which measure synchrony. In the present study, we used a band-pass filter around the 0.008-0.09 Hz range for all BOLD analyses, which is the default for connectivity analyses in CONN, hence allowing better comparability between measures. The main difference between ALFF and fALFF measures lies in the resilience of the latter to the noisy fluctuations from large blood vessels, and in more robust measures regardless of head motion, although we here applied the same preprocessing as for connectivity analyses, which should reduce the impact of motion on ALFF as suggested in previous studies (Turner *et al.*, 2013).

Statistical results were generated with CONN 17f and considered significant with multiple comparison correction at the topological level with non-parametric permutation test cluster-mass p-False Discovery Rate (FDR) <0.05 and with primary voxel-wise threshold p-uncorrected <0.001.

## 5. Results

### 5.1. Quality control assessment

Patients' lesions were accounted for: 1) directly by excluding patients with extensive brain lesions that would either prevent proper segmentation or may impair the inference (three patients were discarded for this reason); 2) indirectly by relying on aCompCor denoising, which ensures we derive most of the signal used for inference from the neuronal components in the signal from segmented grey matter, while regressing non-neuronal

signal from non grey matter tissues, which indirectly includes lesions. For the latter to work as expected, we ensured with visual inspection that there was no anomaly in the segmentation and normalization of the grey matter of all the included subjects. Suppl. Mat. I and II provide figures of the original T1 and segmented grey matter for all participants and for the three excluded patients. Neither patients nor HCS showed a significant difference in the number of motion outliers between music and rest conditions (two-sided paired t-test; patients:  $p=0.42$ , music mean  $\pm$  SD =  $14 \pm 14$ , median (range) = 11 (46); rest mean  $\pm$  SD =  $9 \pm 9$ , median (range) = 7 (31); HCS:  $p=0.31$ , music mean  $\pm$  SD =  $23 \pm 17$ , median (range) = 21 (54); rest mean  $\pm$  SD =  $19 \pm 19$ , median (range) = 13 (51)). No significant difference was found between patients and HCS for the rest ( $p=0.20$ ) and for the music condition ( $p=0.21$ ). The highest observed percentage of motion outliers was 18.3% in one HCS and 15.6% in one patient. The percent of motion outliers related to the totality of volumes per subject and session can be found in Suppl. Mat.III. Finally, the histograms of connectivity provided by CONN at the denoising step are available in Suppl. Mat. IV.

### 5.2. Network-to-voxel analysis of consciousness-level-dependent changes in connectivity

Within the music condition, consciousness-level-dependent increases of connectivity were found in the FPN and in the DMN (Figure 1 & Suppl. Mat. VI). In the FPN, such increases of connectivity were found with four clusters covering: a) the left angular gyrus, b) the left frontal pole, c) the right middle frontal gyrus, and d) the right frontal pole. In the DMN, we identified consciousness-level-dependent increases of connectivity with three clusters covering: a) the left lateral occipital cortex, b) the left posterior cingulate gyrus/precuneus, and c) the left inferior frontal gyrus (pars orbitalis). No significant consciousness-level-dependent increase of connectivity was found for the auditory network (with or without visual areas) and music-evoked emotions network.

During rest, consciousness-level-dependent changes in connectivity were only observed within the DMN (Figure 1 & Suppl. Mat. VI). This network showed an increase of connectivity with three clusters covering: a) the left posterior cingulate gyrus/precuneus, b) the left hippocampus, and c) the right middle temporal gyrus.

Looking at effect sizes of both conditions separately, we observe a linear gradation of the connectivity increase along with the level of consciousness (from (E)MCS to HCS), except for the group of UWS who appears to present a hyperconnectivity (Suppl. Mat. VII, VIII, IX). This linear gradation is most marked for the FPN.

[FIGURE 1]

When comparing the music to the rest condition, consciousness-level-dependent changes in connectivity were found for the FPN with one cluster located in the precuneus/PCC (Figure 2a & Suppl. Mat. VI). No significant difference between the two conditions was observed for any of the other networks.

Looking at effect sizes, we observe that the difference of connectivity between the two conditions seems to be driven by the group of (E)MCS, while the other groups remain constant (Figure 2b).

[FIGURE 2]

### 5.3. Voxel-to-voxel analysis of consciousness-level-dependent changes

#### 5.3.1. Intrinsic connectivity (ICC)

During the music condition, analysis revealed a consciousness-level-dependent increase of intrinsic connectivity (Figure 3a & Suppl. Mat. X) in seven clusters covering: a) the left lateral occipital cortex, left angular gyrus and left supramarginal gyrus, b) the left inferior and middle temporal gyrus, c) the left supramarginal gyrus, d) the precuneus, e) the right inferior frontal gyrus (pars triangularis) and frontal operculum, f) the left supramarginal gyrus, and g) the left middle frontal.

During the rest condition, consciousness-level-dependent increases of intrinsic connectivity were found in two clusters covering: a) the left middle temporal gyrus, and b) precuneus (Figure 3a & Suppl. Mat. X.).

Looking at effect sizes of each condition separately, we observe the same pattern that was previously observed in the network-to-voxel analyses of rest and music conditions alone.

The connectivity increases along with the level of consciousness from (E)MCS to HCS, while the group of UWS presents a hyperconnectivity (Suppl. Mat. X, XI, XII).

No significant results were found when the music condition was compared to the rest condition.

### **5.3.2. Amplitude of Low-Frequency fluctuation (ALFF)**

During the music condition, consciousness-level-dependent increases in ALFF were found in nine clusters (Figure 3b and Suppl. Mat. X.) covering: a) the posterior cingulate gyrus, b) the precuneus, c) the left frontal pole, d) the left planum polare and temporal pole, e) the left inferior temporal gyrus, f) the left parahippocampal gyrus, g) the left middle temporal gyrus, h) the brainstem and i) the left inferior temporal gyrus.

During the rest condition, consciousness-level-dependent increases in ALFF were observed in four clusters covering: a) the left posterior cingulate gyrus, b) the left frontal pole, c) the right supramarginal gyrus, and d) the left frontal pole (Figure 3b & Suppl. Mat. X.).

Looking at the effect sizes of both conditions separately, a linear gradation of the activity along with the level of consciousness (from (E)MCS to HCS) is once again observed for all the clusters, while a hyper-activity is observed for UWS patients.

When comparing the music condition to the rest condition, consciousness-level-dependent increases in ALLF were observed in nine clusters covering: a) the brainstem, b) the vermis, c) the right temporal pole, d) the brainstem, e) the left inferior and middle temporal gyrus, f) the left angular gyrus, g) the left posterior inferior temporal gyrus, h) the left temporal pole and insular cortex, and i) the left middle temporal gyrus (Figure 3b & Suppl. Mat. X.). Looking at the effect sizes, we see that the (E)MCS and LIS groups are the one driving the changes in ALFF between the two conditions. Across most of the clusters, (E)MCS patients either stay constant or have decreased ALFF, while LIS patients either stay constant or have increased ALFF (Figure 4).

No consciousness-level-dependent increases in fALFF were found.

[FIGURE 3]

[FIGURE 4]

## 6. Discussion

In the present study, we explored the effects of preferred music on brain functional connectivity in relation to consciousness. Among the four investigated networks (network-to-voxel analysis), the FPN (also known as task-positive, or external network) was the only one showing stronger consciousness-level-dependent increases of connectivity in the music compared to the rest condition. This stronger relationship to consciousness during preferred music was found in the precuneus, which is known to be especially important in internal awareness (Stewart *et al.*, 2006) as well as episodic memory (Fletcher *et al.*, 1995). The precuneus also plays a key role in music processing and visual imagery (Nakamura *et al.*, 1999). While the current study could not find any consciousness-related functional connectivity changes for the FPN in the rest condition alone (contrary to previous studies : Demertzi *et al.*, 2014, 2015), several regions showed connectivity increases during the music condition. During music, connectivity with the left angular gyrus, the frontal pole and the right middle frontal gyrus showed a relation to consciousness. The angular gyrus is well-known for its role in episodic memory, and may therefore intervene in the recognition of music and the recall of personal associated memories evoked by music (Bonnici *et al.*, 2018). In healthy subjects for example, the angular gyrus showed increased functional connectivity during an imagined music performance task (Tanaka and Kirino, 2019). In addition, this region was shown to be involved in language processing in patients with DOC (Aubinet *et al.*, 2020), which might be related to the processing of lyrics. Moreover, right frontal activity has previously been related to the processing of mode and tempo (Khalifa *et al.*, 2005) and is strongly associated with emotional processing (Bidelman, 2013). Overall, the regions showing consciousness-level related increases in connectivity during music have previously been observed to relate to consciousness in larger studies within classical rest conditions (Demertzi *et al.*, 2015).

Functional connectivity with the DMN showed a relation to the level of consciousness both in the rest and music conditions, although no significant difference was found between the two conditions. Both conditions individually showed increased connectivity in the precuneus and parts of the posterior cingulate gyrus. In the rest condition,

connectivity increases were also observed in the left hippocampus and right middle temporal gyrus. These results are consistent with previous findings of increased DMN connectivity (Vanhaudenhuyse *et al.*, 2010) and decreased ICC and entropy (Luppi *et al.*, 2019) in proportion to the level of consciousness in brain-injured patients. Furthermore, several regions showed increased connectivity only in the music condition: the left lateral occipital cortex and the left inferior frontal gyrus. These regions have all been related to musical processing; connectivity of the lateral occipital cortex and precuneus are related to musical training (Tanaka and Kirino, 2016), while the inferior frontal gyrus is involved in the recognition of familiar melodies (Sato *et al.*, 2006).

Whole brain functional connectivity results (ICC) are in line with those of the network-level analysis mentioned above. The music and rest conditions independently showed significant connectivity increases as a function of the level of consciousness in the middle temporal gyrus and precuneus. In the music condition, stronger connectivity as a function of consciousness was also observed in multiple regions already highlighted in the network-to-voxel analyses, namely those involved in language and semantic processing (i.e., the left angular gyrus, left supramarginal gyrus, left lateral occipital cortex, left inferior temporal gyrus) (Visser *et al.*, 2010). Besides these areas, the right inferior frontal gyrus and the right frontal operculum were also found to have stronger connectivity as a function of consciousness in the music condition. These two regions are known to be involved in music processing, respectively in the perception of the emotional content of music (Tabei, 2015), and in pitch processing and melody generation (Stewart *et al.*, 2006).

In addition to the investigation of functional connectivity, we also probed the potential positive changes that music could induce on the magnitude of brain regional spontaneous activity. When comparing music to rest, we found increasing ALFF (but not fALFF) in the brainstem, the vermis, the temporal pole, the left inferior and middle temporal gyrus, left insular cortex and the left angular gyrus, all of which are music-related brain areas. For example, the cerebellar vermis and the brainstem are important in musical temporal structure processing (Levitin, 2009; Bidelman, 2013), the insular cortex is involved in pleasant and familiar music processing (Stewart *et al.*, 2006; Koelsch, 2014), the middle temporal gyrus is known to play a role in auditory and linguistic processing, as well as music memory (Binder *et al.*, 1996; Watanabe *et al.*, 2008), and the inferior temporal



gyrus is involved in stimulus recognition (Buckley *et al.*, 1997). Similarly to the connectivity analysis, both the rest and music conditions individually showed regions of activation in relation to consciousness (see Figure 3 & Suppl. Mat. X.). Furthermore, consciousness-level-dependent changes in activity are again found more substantial during the music condition than during the rest condition. In line with the above-mentioned results, all regions of increased activity can be related to musical processing. On the other hand, the absence of significant results with fALFF must urge us to consider the results from ALFF with the greatest caution (Mao *et al.*, 2015). For this reason, future studies should replicate these results to investigate if the presence of results with ALFF but not with fALFF might imply that noise is being measured instead of the signal.

With a partial reanalysis of patients' data (Heine *et al.*, 2015) we provide further relevant insights on the importance of preferred stimuli during assessment of patients' cognitive capacity. The results converge furthermore with previous studies and provide evidence that music might potentially trigger activity and connectivity changes more substantially compared to a rest condition without any sensory stimulation. These effects are mostly observed in brain regions involved in consciousness, episodic memory, but also in auditory, language and emotion processing. Moreover, the effect sizes of the significant results provide us additional insights, showing that the difference in connectivity observed between the two conditions in the FPN (with the precuneus) is mostly driven by a decrease of connectivity in (E)MCS patients. We expect this observed decrease in connectivity to be due to stronger anticorrelations in EMCS patients. Previous research has shown that anticorrelations are observable with the FPN in EMCS patients, but not in MCS and UWS (Di Perri *et al.*, 2016). However, the observed effects could also be due to a decrease of positive connectivity or even a reorganization of cerebral networks. Regarding ALFF, a music-induced effect is also identifiable, with a wide decrease in activity in several regions observed in (E)MCS and an increase in LIS patients. Although these findings have to be taken and interpreted with caution due to our small sample size, we did not find any substantial changes in UWS and HCS in terms of connectivity or activity due to preferred music. These effects of music therefore could only be observed in severely brain-injured patients with some preserved awareness. The absence of effect in HCS is in line with the findings of two previous studies (Castro *et al.*, 2015; Heine *et al.*, 2015). To explain the

absence of effect in HCS, these studies hypothesized that the cerebral responses of the HCS cannot be enhanced because they are already at ceiling, or because of the control condition, which would be too neutral to observe a difference with the music condition. Alternatively, it is possible that the effect of music on HCS may be more subtle than the response evoked in brain-injured patients (who experience a reduction of sources of stimulations due to their condition, and hence may be more sensitive to stimuli such as music), which would require a bigger sample size to observe. Finally, in all our results, the group of UWS seems to present a constant hyper-connectivity/activity, whether during the music or the rest condition. In the absence of any difference between the two conditions we can conclude that music does not seem to trigger any stronger effect on UWS patients. Even if this pattern is surprising, it is however not without precedent since other studies also evidenced hyperconnectivity in these patients (Di Perri *et al.*, 2013, 2016; Wu *et al.*, 2015). One hypothesis would be a persistent engagement of residual neural activity in self-reinforcing neural loops which, in turn, might disrupt normal patterns of connectivity.

Our study has several limitations. Due to the experiment design, only patients that were not sedated, remained calm enough, and had close relatives who knew their favorite music could be included, leading to a small sample size. The low number of patients and its heterogeneity prevents from making strong assumptions or generalizing the findings. However, the obtained results are in line with previous studies on music interventions in DOC (Grimm and Kreutz, 2018). Moreover, our sample was divided in four groups: unconsciousness, fluctuating consciousness, LIS and normal consciousness. Further studies should therefore focus on exploring potential effects within the minimally conscious population. Furthermore, we decided to include LIS patients in our gradient of consciousness, placing them between MCS-EMCS and HCS. Although, by definition, LIS have relatively preserved cognitive capabilities, our two LIS patients presented below-standard performance in neuropsychological tests evaluating visual memory, executive functions, language and sustained attention. We therefore postulated that they could present stronger music related effects compared to HCS, which generally show no effect of music (Castro *et al.*, 2015; Heine *et al.*, 2015). Finally, the study employs preferred

music because of the beneficial effects of preferred music demonstrated in other pathologies such as stroke (Soto *et al.*, 2009), and those of salient stimuli on DOC patients. We assumed preference can maximize the effect of music on brain function. However, it is entirely possible that the observed effects are not due to the preference itself and we cannot draw conclusions as to which properties of (preferred) music we can attribute the effects. Even though the chosen music was vastly different within and between subjects, the results could indeed be due to the structural and acoustic features of the musical pieces. Furthermore, our findings are in line with both of the existing theories explaining the beneficial effect of music at present, namely the "Mood and arousal hypothesis" (Nantais and Schellenberg, 1999), and the autobiographical priming (Castro *et al.*, 2015). Further research should focus on effects of music in general and its specific acoustic features as well as simple auditory stimuli. Future studies should also explore the effect of preference to distinguish between the current theories. In this context, the exploration of the salience network might also be of interest.

In conclusion, music seems to enhance brain functioning by strengthening the connectivity and increasing regional spontaneous activity of a wide range of subcortical and cortical brain regions in a conscious-level dependent manner. These results constitute an indication of stronger musical processing in higher states of consciousness. They could also point towards the ability of music to temporarily stimulate patients' brain functions. Overall, although our results should be taken with caution given the small sample size and the heterogeneity of patients' clinical condition, they seem to be in favor of the hypothesis that music could play a role in improvements of diagnostic assessment.

### **Authors Contributions**

LH, FP, CM and MC conceived, planned, and conducted the research and analyses. MC, SKL, LH and CM interpreted the results. SKL and MB designed the methods and scripts for data preprocessing and analysis on fMRI. MC and SKL realized the visualizations. LH, MC, CA and CM carried the data acquisitions. CM and LH provided guidance and supervision on the whole study. SL provided supervision and resources. MC, SKL, and LH drafted the manuscript and all authors provided critical feedback and helped shape the final

manuscript. SKL and CA are FRS-FNRS research fellows, and SL is research director at FRS-FNRS.

### **Acknowledgments**

The authors thank the patients and their families for participating in this study, as well as Dr J.-F.L.Tshibanda, Mr J.Klein, Mrs N.Maquet, Mr J.-M. Léonard and the whole staff from the Neurology, Radiodiagnostic and Nuclear Medicine departments, University Hospital of Liège, the Cyclotron of the University of Liège, the Siemens Healthineers, and Pr A.Nieto-Castanon of the Department of Speech, Language, and Hearing sciences, Boston University (USA) for their kind technical support and advices. We also thank the reviewers who provided excellent feedback.

### **Author Disclosure Statement**

No competing financial interests exist.

## References

- Aubinet C, Cassol H, Gosseries O, Bahri MA, Larroque SK, Majerus S, et al. Brain metabolism but not grey matter volume underlies the presence of language function in the minimally conscious state (MCS): MCS+ versus MCS- Neuroimaging differences. *Neurorehabil Neural Repair* 2020; 1545968319899914.
- Behzadi Y, Restom K, Liu J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage* 2007; 37: 90–101.
- Bidelman GM. The role of the auditory brainstem in processing musically relevant pitch. *Front Psychol* 2013; 4: 1–13.
- Binder JR, Frost JA, Hammeke TA, Rao SM, Cox RW. Function of the left planum temporale in auditory and linguistic processing. *Brain* 1996; 119: 1239–1247.
- Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. *Lancet Neurol* 2008; 7: 1013–1020.
- Bonnici HM, Cheke LG, Green DAE, FitzGerald THMB, Simons JS. Specifying a causal role for angular gyrus in autobiographical memory. *J Neurosci* 2018; 38: 10438–10443.
- Buckley MJ, Gaffan D, Murray EA. Functional double dissociation between two inferior temporal cortical areas: Perirhinal cortex versus middle temporal gyrus. *J Neurophysiol* 1997; 77: 587–598.
- Castro M, Tillmann B, Luaute J, Corneyllie A, Dailler F, Andre-Obadia N, et al. Boosting Cognition With Music in Patients With Disorders of Consciousness. *Neurorehabil Neural Repair* 2015; 29: 734–742.
- Cheng L, Gosseries O, Ying L, Hu X, Yu D, Gao H, et al. Assessment of localisation to auditory stimulation in post-comatose states: Use the patient's own name. *BMC Neurol* 2013; 13

Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, De Los Angeles C, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. *Brain* 2015; 138: 2619–2631.

Demertzi A, Gómez F, Crone JS, Vanhaudenhuyse A, Tshibanda L, Noirhomme Q, et al. Multiple fMRI system-level baseline connectivity is disrupted in patients with consciousness alterations. *Cortex* 2014; 52: 35–46.

Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Gosseries O, Soddu A, et al. Attitudes towards end-of-life issues in disorders of consciousness: A European survey. *J Neurol* 2011; 258: 1058–1065.

Fletcher P., Frith C., Baker S., Shallice T, Frackowiak RS., Dolan R. The mind's eye—precuneus activation in memory-related imagery. *Neuroimage* 1995; 2: 195–200.

Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: Definition and diagnostic criteria. *Neurology* 2002; 58: 349–353.

Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004; 85: 2020–2029.

Grimm T, Kreutz G. Music interventions in disorders of consciousness (DOC)—a systematic review. *Brain Inj* 2018; 32: 704–714.

Heine L, Castro M, Martial C, Tillmann B, Laureys S, Perrin F. Exploration of functional connectivity during preferred music stimulation in patients with disorders of consciousness. *Front Psychol* 2015; 6: 1–11.

Heine L, Soddu A, Gómez F, Vanhaudenhuyse A, Tshibanda L, Thonnard M, et al. Resting state networks and consciousness Alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness states. *Front Psychol* 2012; 3: 1–12.

Khalifa S, Schon D, Anton JL, Liégeois-Chauvel C. Brain regions involved in the recognition of happiness and sadness in music. *Neuroreport* 2005; 16: 1981–1984.

Koelsch S. Brain correlates of music-evoked emotions. *Nat Rev Neurosci* 2014; 15: 170–180.

Levitin DJ. The Neural Correlates of Temporal Structure in Music. *Music Med* 2009; 1: 9–13.

Luppi AI, Craig MM, Finoia P, Williams GB, Naci L, Menon DK, et al. Consciousness-specific dynamic interactions of brain integration and functional diversity. *Nat Commun* 2019; 10: 1–12.

Magee WL. Music therapy with patients in low awareness states: Approaches to assessment and treatment in multidisciplinary care. *Neuropsychol Rehabil* 2005; 15: 522–536.

Mao D, Ding Z, Jia W, Liao W, Li X, Huang H, et al. Low-frequency fluctuations of the resting brain: High magnitude does not equal high reliability. *PLoS One* 2015; 10: 1–20.

Nakamura S, Sadato N, Oohashi T, Nishina E, Fuwamoto Y, Yonekura Y. Analysis of music-brain interaction with simultaneous measurement of regional cerebral blood flow and electroencephalogram beta rhythm in human subjects. *Neurosci Lett* 1999; 275: 222–226.

Nantais KM, Schellenberg EG. The mozart effect: An Artifact of Preference. *Psychol Sci* 1999; 10: 370–373.

Okumura Y, Asano Y, Takenaka S, Fukuyama S, Yonezawa S, Kasuya Y, et al. Brain activation by music in patients in a vegetative or minimally conscious state following diffuse brain injury. *Brain Inj* 2014; 9052: 1–7.

Di Perri C, Bahri MA, Amico E, Thibaut A, Heine L, Antonopoulos G, et al. Neural correlates of consciousness in patients who have emerged from a minimally conscious state: A cross-sectional multimodal imaging study. *Lancet Neurol* 2016; 15: 830–842.

Di Perri C, Bastianello S, Bartsch AJ, Pistarini C, Maggioni G, Magrassi L, et al. Limbic hyperconnectivity in the vegetative state. *Neurology* 2013; 81: 1417–1424.

Perrin F, Castro M, Tillmann B, Luauté J. Promoting the use of personally relevant stimuli for investigating patients with disorders of consciousness. *Front Psychol* 2015; 6: 1–9.

Raglio A, Guizzetti GB, Bolognesi M, Antonaci D, Granieri E, Baiardi P, et al. Active music therapy approach in disorders of consciousness: a controlled observational case series. *J Neurol* 2014; 261: 2460–2462.

Satoh M, Takeda K, Nagata K, Shimosegawa E, Kuzuhara S. Positron-emission tomography of brain regions activated by recognition of familiar music. *Am J Neuroradiol* 2006; 27: 1101–1106.

Schiff ND. Cognitive motor dissociation following severe brain injuries. *JAMA Neurol* 2015; 72: 1413–1415.

Schnakers C, Majerus S, Goldman S, Boly M, Van Eeckhout P, Gay S, et al. Cognitive function in the locked-in syndrome. *J Neurol* 2008; 255: 323–330.

Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 2009; 9: 1–5.

Soto D, Funes MJ, Guzmán-García A, Warbrick T, Rotshtein P, Humphreys GW. Pleasant music overcomes the loss of awareness in patients with visual neglect. *Proc Natl Acad Sci U S A* 2009; 106: 6011–6.

Stewart L, Von Kriegstein K, Warren JD, Griffiths TD. Music and the brain: Disorders of musical listening. *Brain* 2006; 129: 2533–2553.

Sun Y, Wang J, Heine L, Huang W, Wang J, Hu N, et al. Personalized objects can optimize the diagnosis of EMCS in the assessment of functional object use in the CRS-R: A double blind, randomized clinical trial. *BMC Neurol* 2018; 18: 1–5.

Tabei K. Inferior Frontal Gyrus Activation Underlies the Perception of Emotions, While Precuneus Activation Underlies the Feeling of Emotions during Music Listening. *Behav Neurol* 2015; 2015: 1–6.



Tanaka S, Kirino E. Functional Connectivity of the Precuneus in Female University Students with Long-Term Musical Training. *Front Hum Neurosci* 2016; 10: 1–7.

Tanaka S, Kirino E. Increased functional connectivity of the angular gyrus during imagined music performance. *Front Hum Neurosci* 2019; 13: 1–8.

The Multi-Society Task Force on PVS. Medical Aspects of the Persistent Vegetative State. *N Engl J Med* 1994; 330: 1499–1508.

Turner JA, Damaraju E, Van Erp TGM, Mathalon DH, Ford JM, Voyvodic J, et al. A multi-site resting state fMRI study on the amplitude of low frequency fluctuations in schizophrenia. *Front Neurosci* 2013; 7: 1–13.

Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJF, Bruno MA, Boveroux P, Schnakers C, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain* 2010; 133: 161–171.

Verger J, Ruiz S, Tillmann B, Ben Romdhane M, De Quelen M, Castro M, et al. Beneficial effect of preferred music on cognitive functions in minimally conscious state patients. *Rev Neurol (Paris)* 2014; 170: 693–699.

Visser M, Embleton K V., Jefferies E, Parker GJ, Ralph MAL. The inferior, anterior temporal lobes and semantic memory clarified: Novel evidence from distortion-corrected fMRI. *Neuropsychologia* 2010; 48: 1689–1696.

Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S. The repetition of behavioral assessments in diagnosis of disorders of consciousness. *Ann Neurol* 2017; 81: 883–889.

Wannez S, Vanhaudenhuyse A, Laureys S, Brédart S. Mirror efficiency in the assessment of visual pursuit in patients in minimally conscious state. *Brain Inj* 2017; 31: 1429–1435.

Watanabe T, Yagishita S, Kikyo H. Memory of music: Roles of right hippocampus and left inferior frontal gyrus. *Neuroimage* 2008; 39: 483–491.

Whitfield-Gabrieli S, Nieto-Castanon A. *Conn* : A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connect* 2012; 2: 125–141.

Wu X, Zou Q, Hu J, Tang W, Mao Y, Gao L, et al. Intrinsic functional connectivity patterns predict consciousness level and recovery outcome in acquired brain injury. *J Neurosci* 2015; 35: 12932–12946.

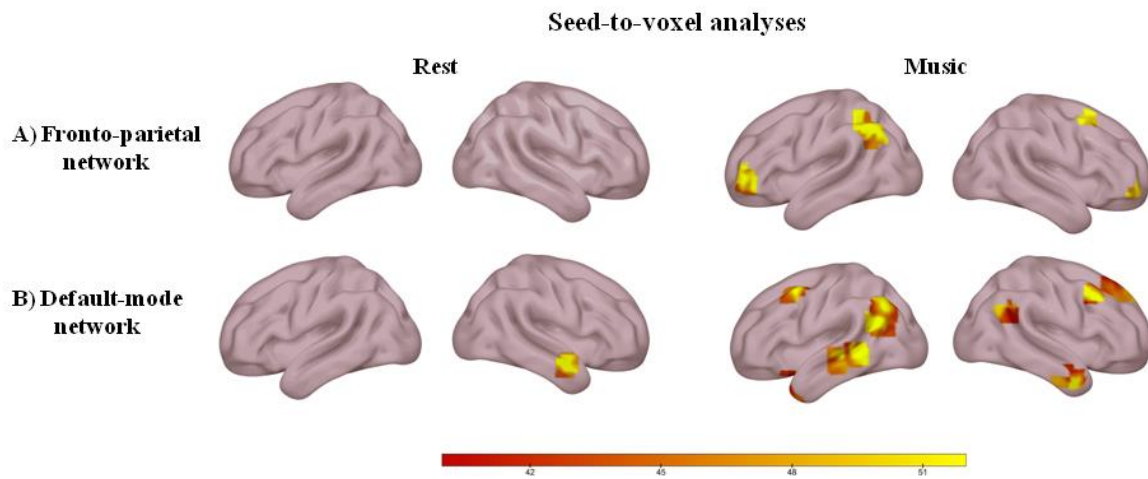
Statistical Parametric Mapping 12 [Internet]. Available from:  
<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>

	<b>Gender</b>	<b>Age (years )</b>	<b>Time since injury (months )</b>	<b>Etiology</b>	<b>Major structural lesions</b>	<b>Best CRS- R score</b>
UWS1	Male	40	11	Trauma	Diffuse axonal lesions in subcortical white matter, temporal poles and hippocampi. Gliotic lesions in the thalami, left pallidum, right caudate nucleus and in the juxtacortical regions of white matter in frontal lobes	A1 V0 M2 O1 C0 Ar1
UWS2	Female	50	6	Anoxia	Extended cortical atrophy in frontomedian, frontoparietal and insulo-temporal	A1 V0 M2 O1 C0 Ar2

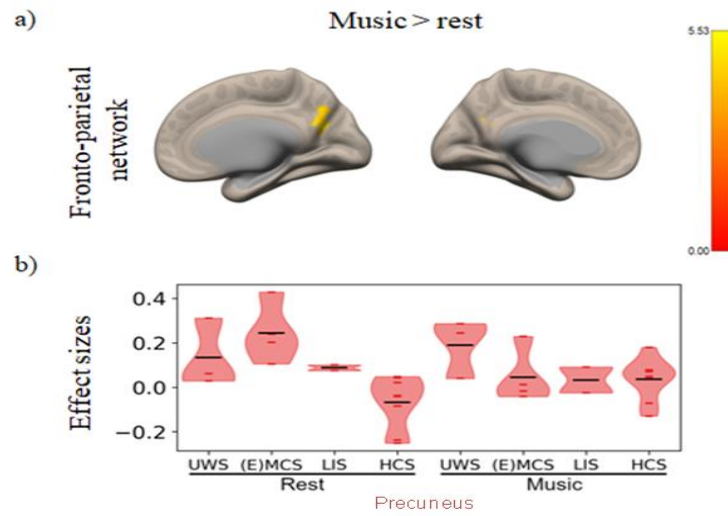
					regions.	
					Subcortical atrophy with enlargement of lateral ventricles.	
UWS3	Male	24	12	Trauma	Diffuse and severe cortical and subcortical atrophy	A1 V1 M2 O1 C0 Ar1
MCS1	Female	39	42	Trauma	White and gray matter damage in the right frontoinsular region, mesio-frontal cortex, thalamus, basal ganglia and hippocampus	A2 V3 M2 O2 C0 Ar1
EMCS 1	Female	43	4	Hemorrhage	Atrophy of dorsal and frontal areas and ventricles hypertrophia	A3 V1 M5 O3 C2 Ar2
EMCS	Male	40	5	Ischemia	Subcortical	A4

2						atrophy	V5
						involving left	M6
						thalamus	O2
							C2
							Ar3
						Extended	
						tissue damage	
						in the	
						posterior	
						cerebral	A4
						artery	V5
EMCS	Male	60	13	Stroke		territory	M6
3						involving the	O3
						thalamus, and	C2
						enlargement	Ar3
						of the right	
						temporal horn	
						of the lateral	
						ventricle	
						Malacic	
						vascular lesion	
						involving a	
						large part of	
						the	
LIS1	Female	65	84	Stroke		protuberance	N/A
						and the upper	
						part of the	
						cord. Focal	
						hyperintense	
						frontobasal	

						focal lesions. Cerebellum atrophy.	
LIS2	Male	50	5	Stroke		Gray matter damage in the cerebellum, hypothalamus , ventromedial cortex, sensorimotor cortex, insula, temporal lobe, and basal ganglia	N/A

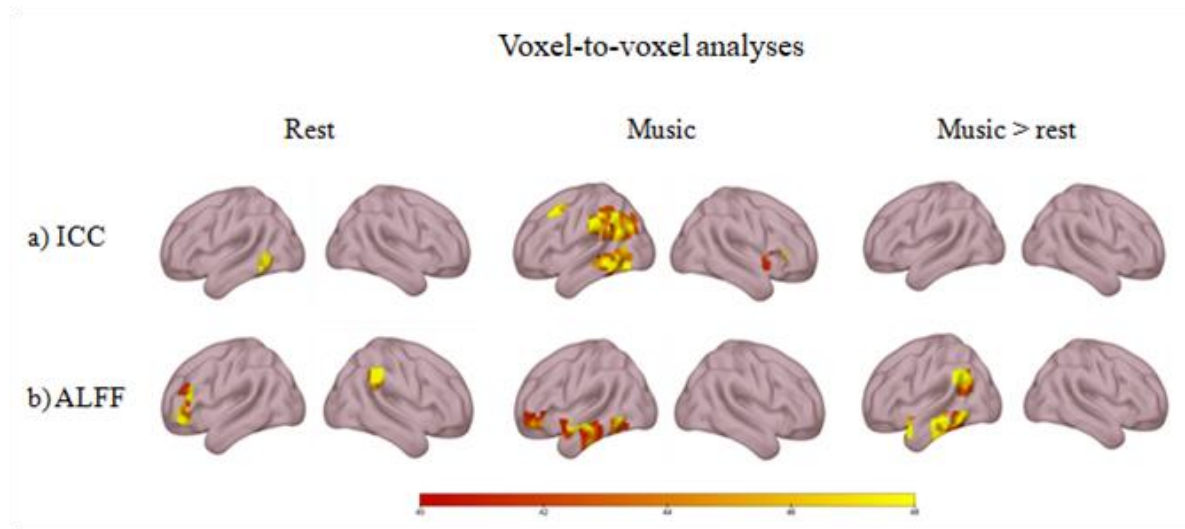


**Figure 1.** Mean network connectivity in patients during the rest condition (on the left) and during the music conditions (on the right) for the fronto-parietal and default-mode networks. Maps show the regions presenting consciousness-level-dependent increases of connectivity. Color-bar indicates the strength of the connectivity.

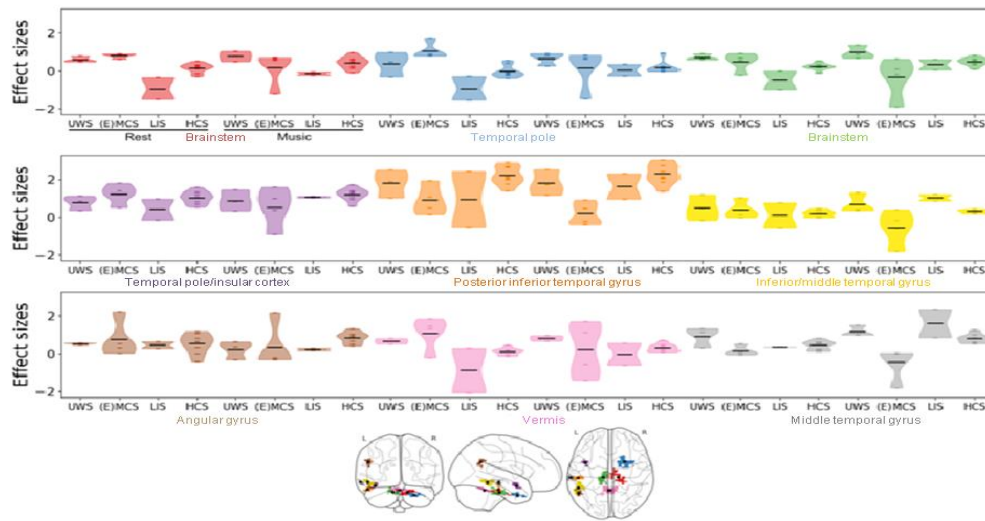


**Figure 2.** a) Mean network connectivity in patients during the music compared to the rest condition for the fronto-parietal network. Maps show the regions with stronger consciousness-level-dependent increases of connectivity. b) Effect sizes (z-values) for the cluster (precuneus) showing increased correlation across consciousness states with the fronto-parietal network in the music compared to the rest condition. The violin plots represent kernel density estimation. Each red dot represents one patient/healthy subject and black lines represent the mean.





**Figure 3.** Voxel-to-voxel analysis of the Intrinsic Connectivity Contrast (a) - ICC) and of the Amplitude of Low-Frequency Fluctuation (b) - ALFF). The maps show brain areas with stronger consciousness-level-dependent increases during the rest condition (on the left), the music condition (in the middle) and during the music compared to the rest condition (on the right).



**Figure 4.** Effect sizes (z-values) for the clusters showing increased ALFF (activity) in the music compared to the rest condition at the whole brain level. The violin plots represent kernel density estimation. Each dot represents one patient/healthy subject and black lines represent the means. Each color represents one cluster.

## SUPPLEMENTARY MATERIALS

**This document includes:**

**Supplementary I.** Original t1 of all HCS/patients included in the study and of the 3 rejected patients.

**Supplementary II.** Segmented grey matter of all HCS/ patients included in the study and of the 3 rejected patients.

**Supplementary III.** Percent of motion outliers related to the totality of volumes per session and per HCS/patient

**Supplementary IV.** Histogram of connectivity for each patient and each healthy subject

**Supplementary V.** Coordinates of all the seeds used for the network-to-voxel analyses.

**Supplementary VI.** fMRI results of network-to-voxel analysis

**Supplementary VII.** Network-to-voxel analysis: fronto-parietal network (music)

**Supplementary VIII.** Network-to-voxel analysis: default mode network (music)

**Supplementary IX.** Network-to-voxel analysis: default mode network (rest)

**Supplementary X.** fMRI results of voxel-to-voxel analysis.

**Supplementary XI.** Voxel-to-voxel analysis: Intrinsic Connectivity Contrast (music)

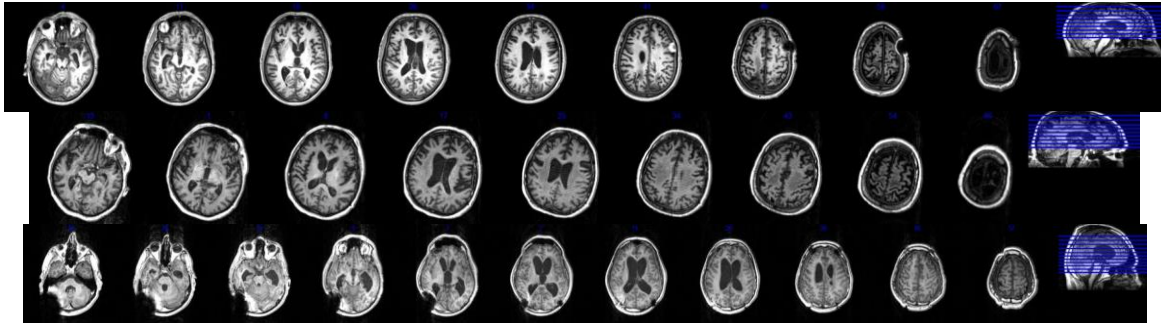
**Supplementary XII.** Voxel-to-voxel analysis: Intrinsic Connectivity Contrast (rest)

**Supplementary XII.** Voxel-to-voxel analysis: Amplitude of Low Frequency Fluctuation (music)

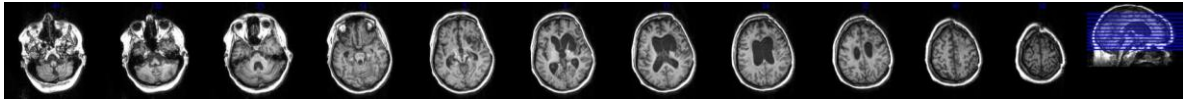
**Supplementary XIV.** Voxel-to-voxel analysis: Amplitude of Low Frequency Fluctuation (rest)

**Supplementary Material I.** Original t1 (multi-slices) of all subjects and patients included in the study, and of the three rejected patients.

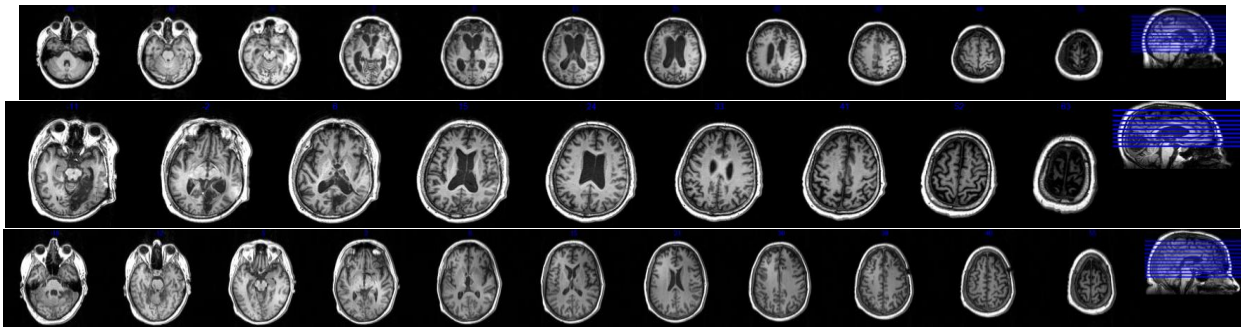
UWS



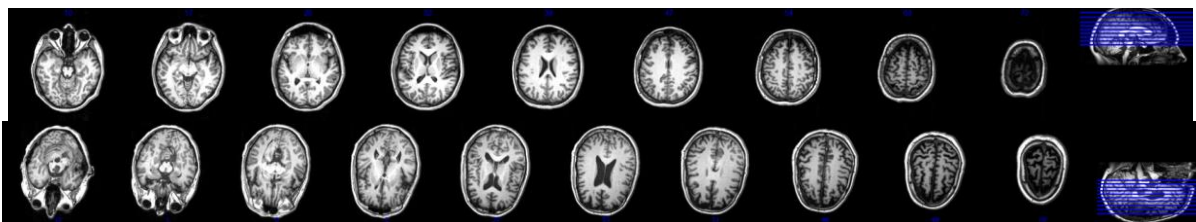
MCS



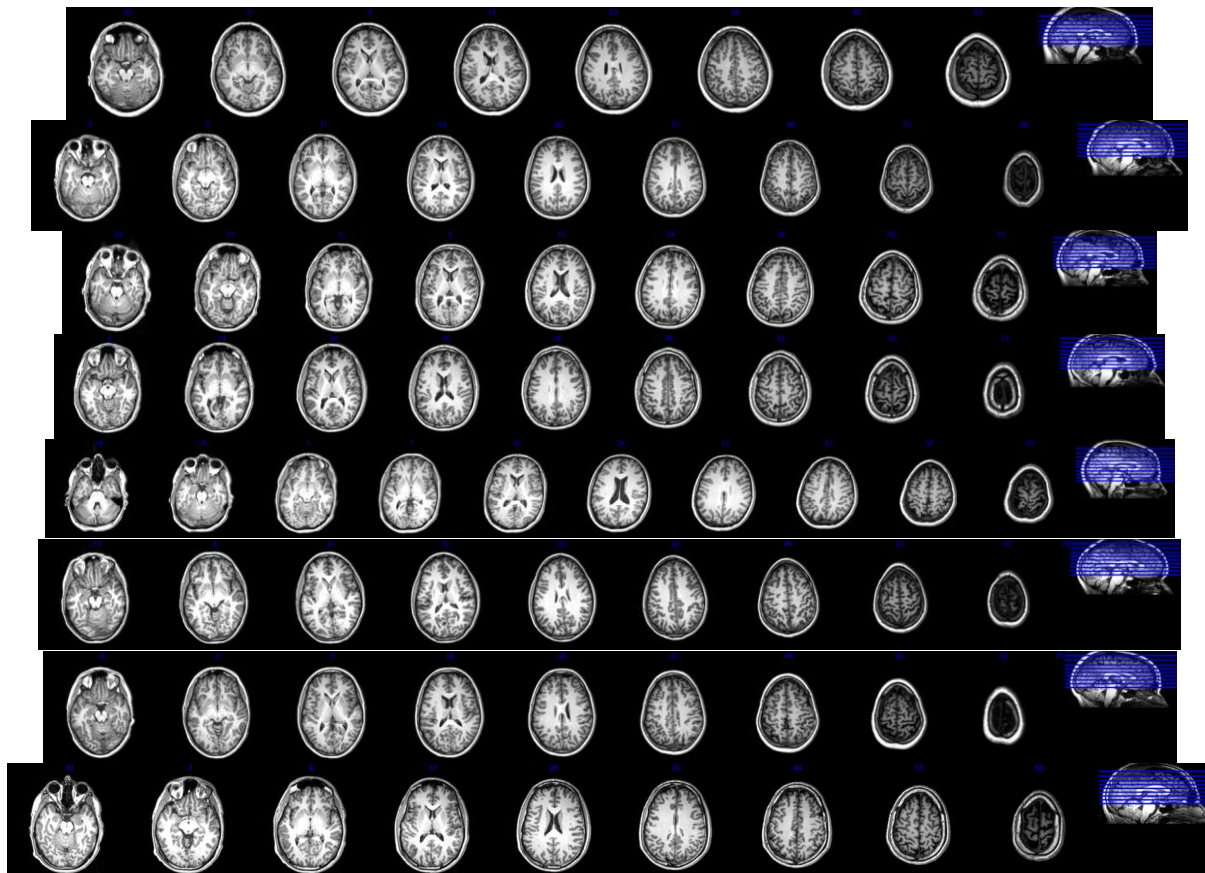
EMCS



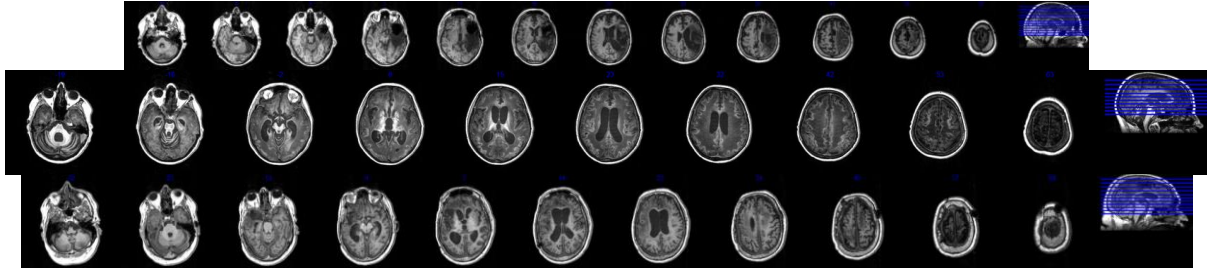
LIS



HCS

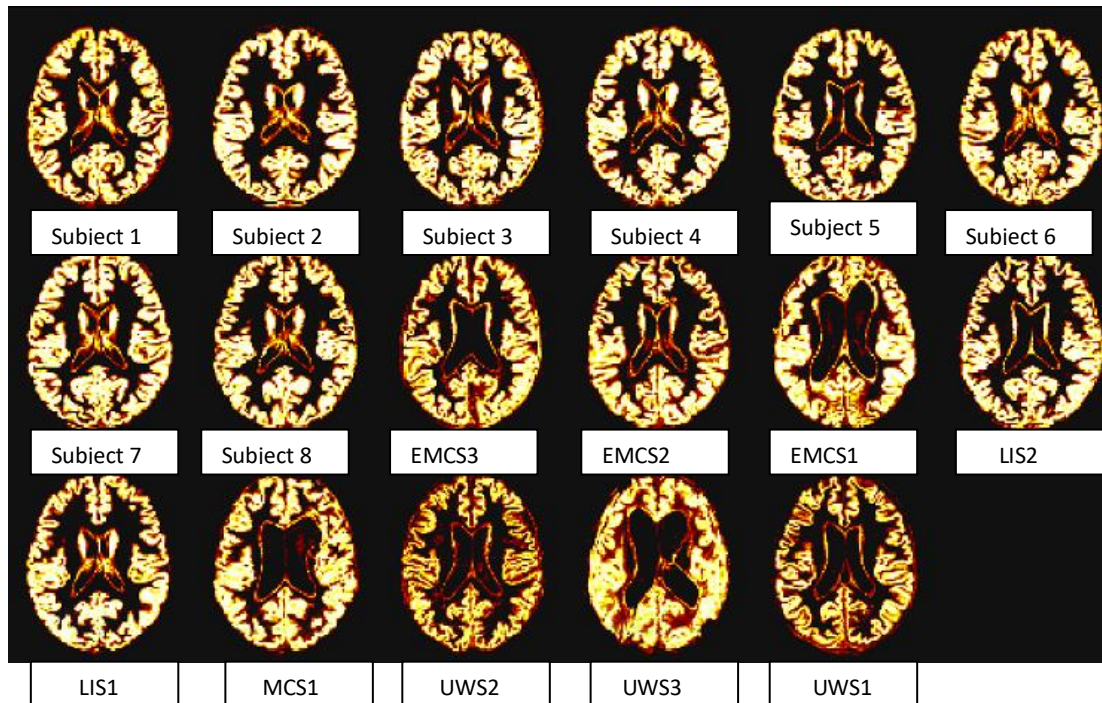


Three rejected patients

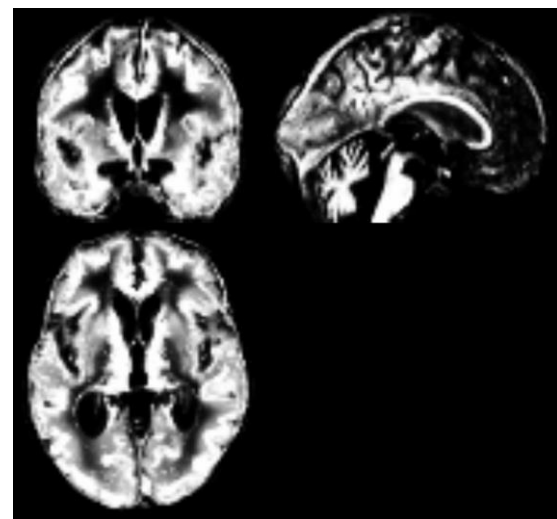
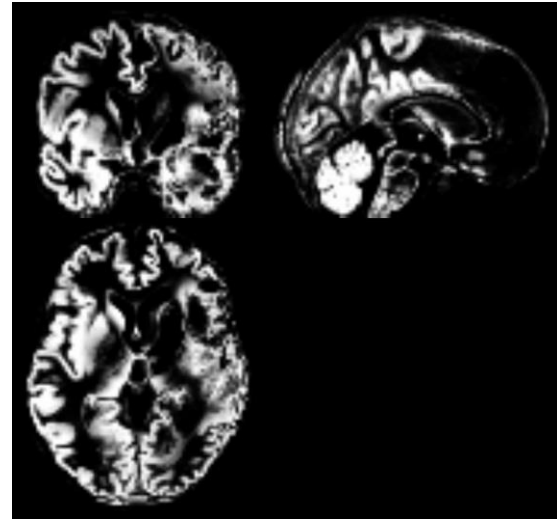
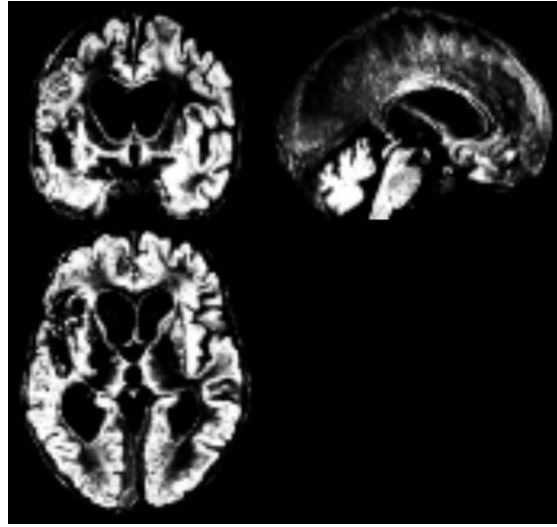




**Supplementary Material II.** Segmented grey matter of all subjects and patients included in the study (above), and of the three rejected patients (below).



Three rejected patients:





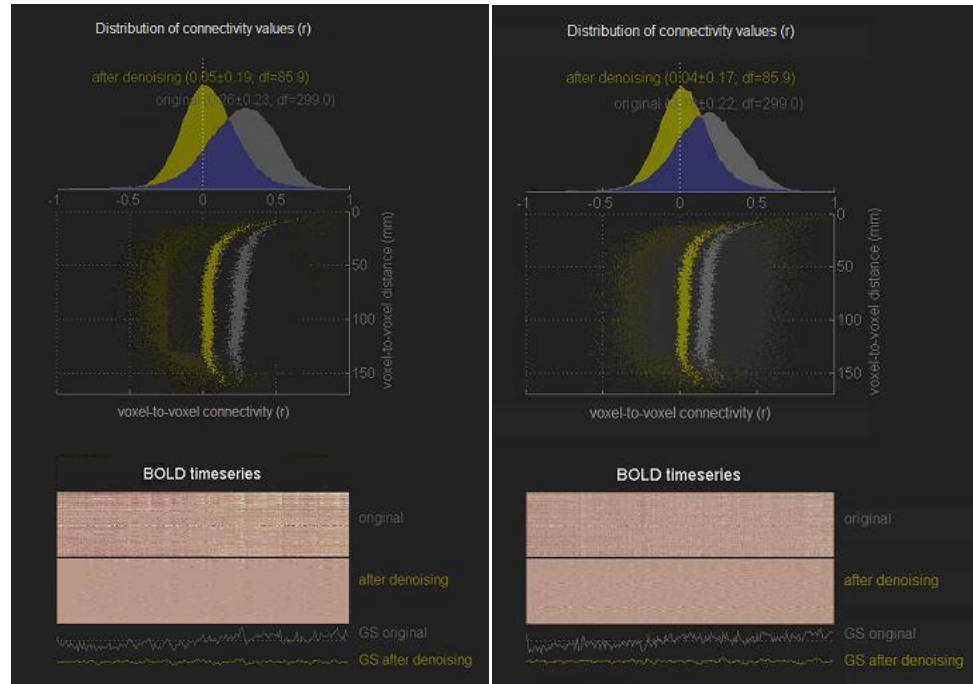
**Supplementary III.** Percent of motion outliers related to the totality of volumes per session and subject/patient

	<b>Rest condition</b>	<b>Music condition</b>
<b>Patient 1</b>	1.6 %	1.6 %
<b>Patient 2</b>	1.6 %	0.3 %
<b>Patient 3</b>	5 %	5 %
<b>Patient 4</b>	2.3 %	1 %
<b>Patient 5</b>	1.6 %	3.6 %
<b>Patient 6</b>	0.3 %	3.6 %
<b>Patient 7</b>	3 %	2.3 %
<b>Patient 8</b>	10.6 %	7.6 %
<b>Patient 9</b>	2.6 %	15.6 %
<b>Subject 10</b>	5 %	2 %
<b>Subject 11</b>	2.3 %	7 %
<b>Subject 12</b>	6.6 %	9.6 %
<b>Subject 13</b>	0.3 %	0.3 %
<b>Subject 14</b>	15.6 %	12 %
<b>Subject 15</b>	1 %	7 %
<b>Subject 16</b>	3.6 %	6.3 %
<b>Subject 17</b>	17.3 %	18.3 %

IV. Histogram of connectivity for each patient and each healthy subject (generated by CONN v17F toolbox).

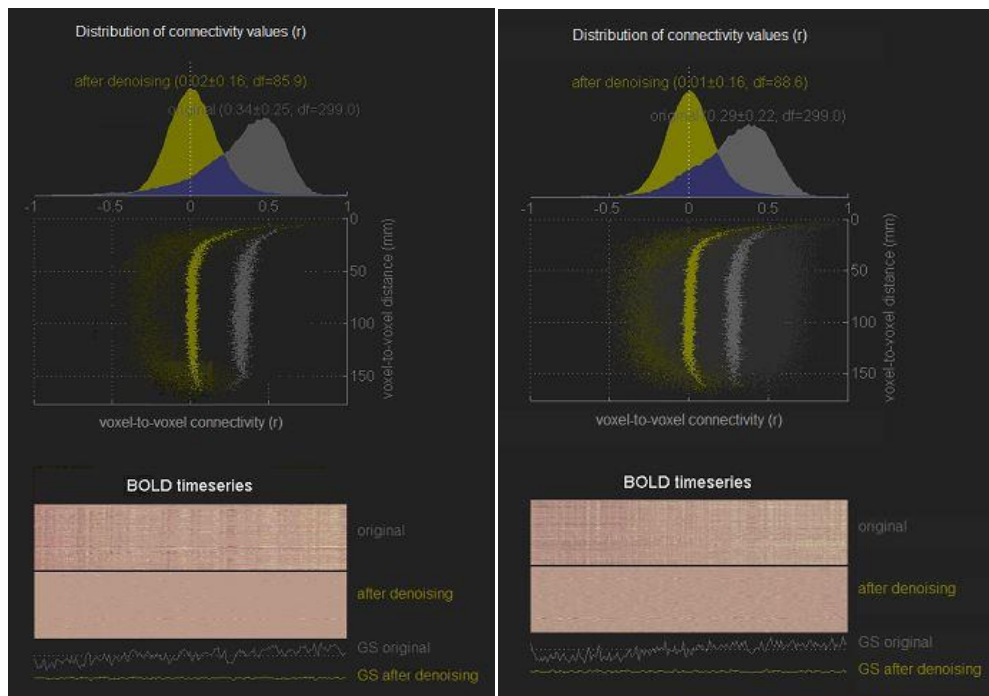
Patient 1 : Rest

Patient 1 : Music



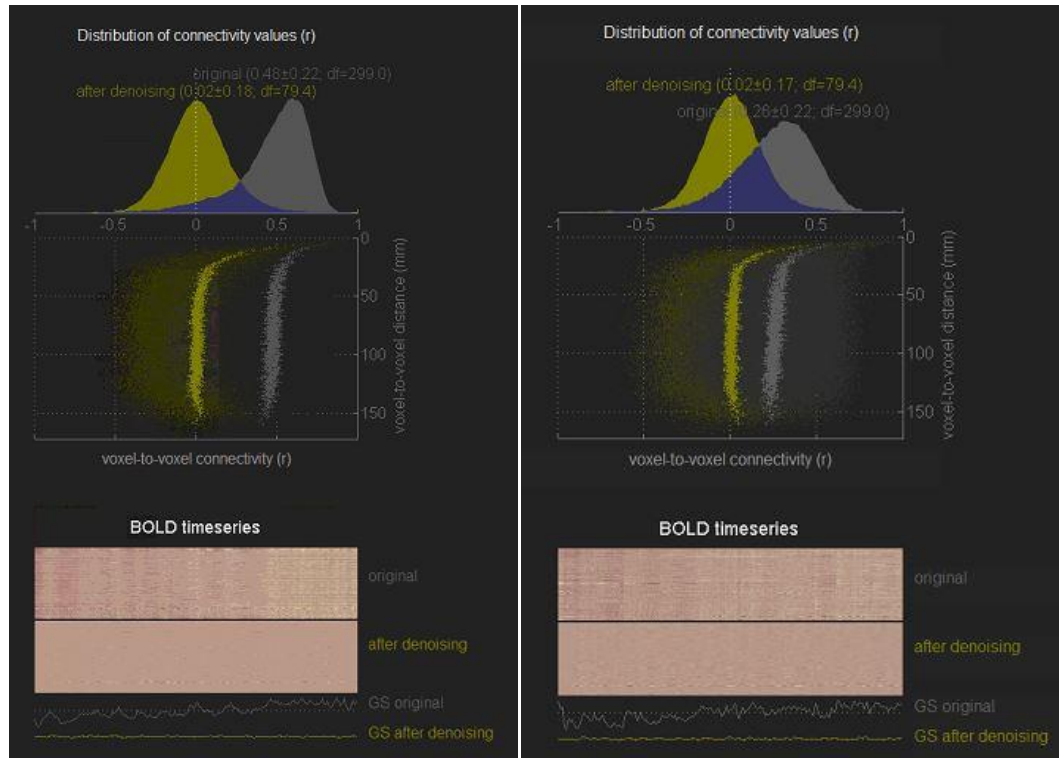
Patient 2 : Rest

Patient 2 : Music



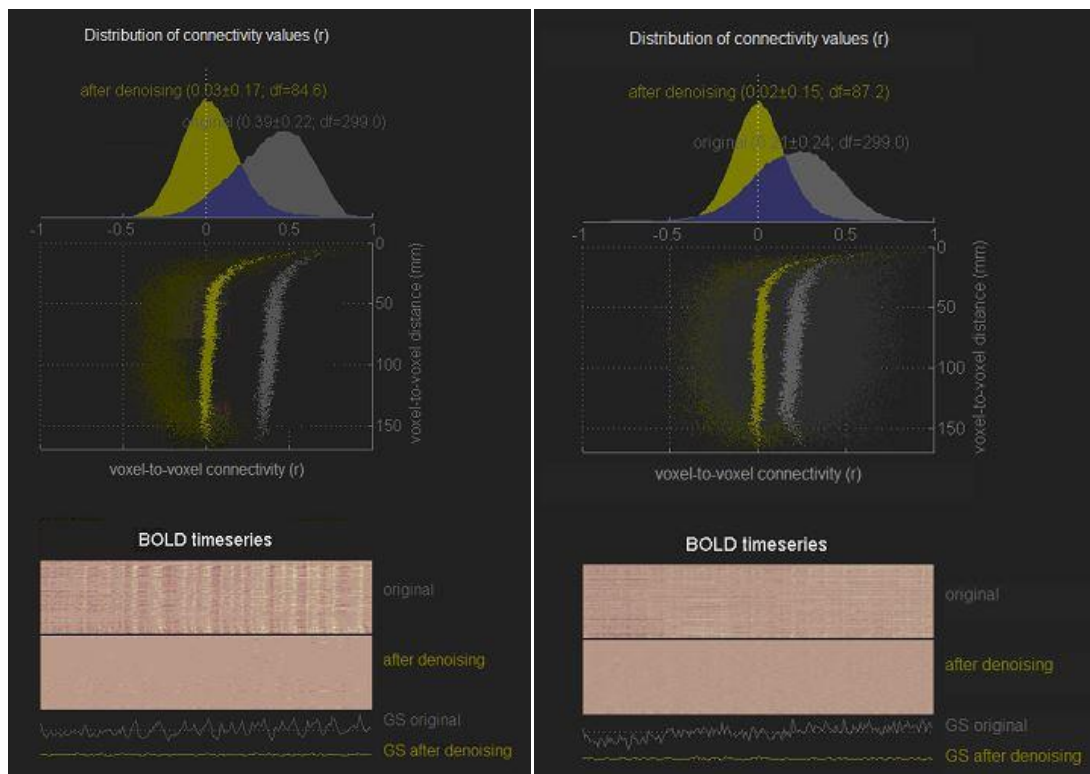
Patient 3 : Rest

Patient 3 : Music



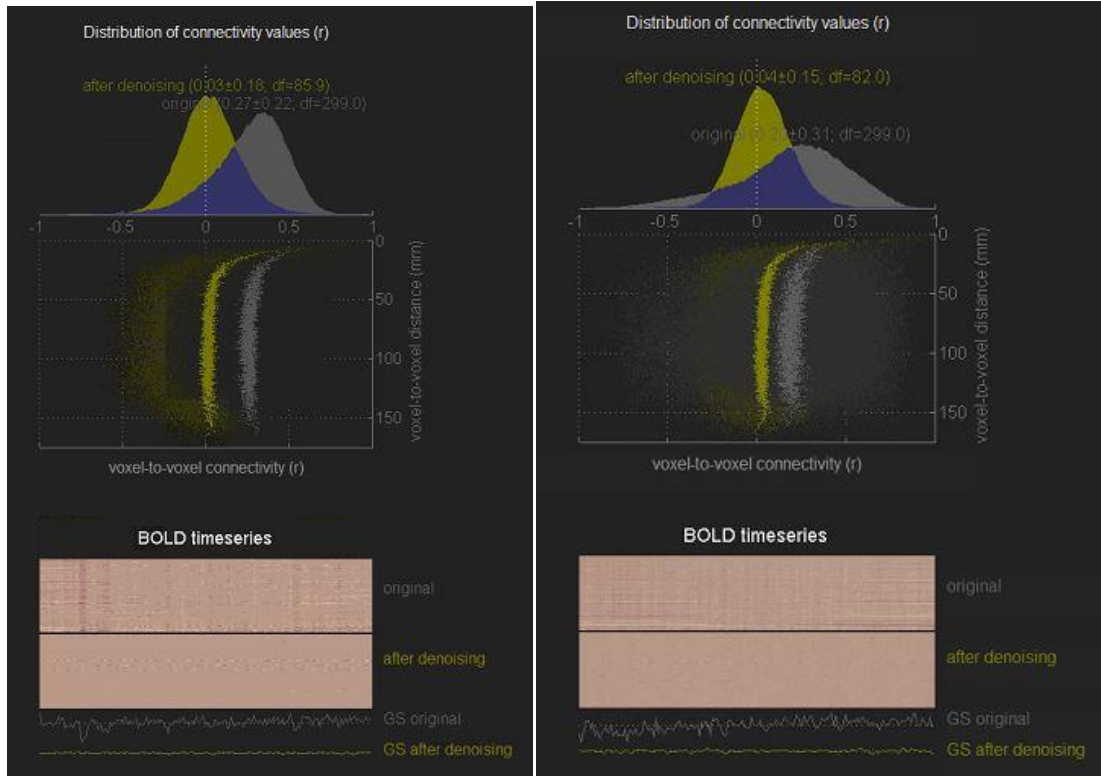
Patient 4 : Rest

Patient 4 : Music



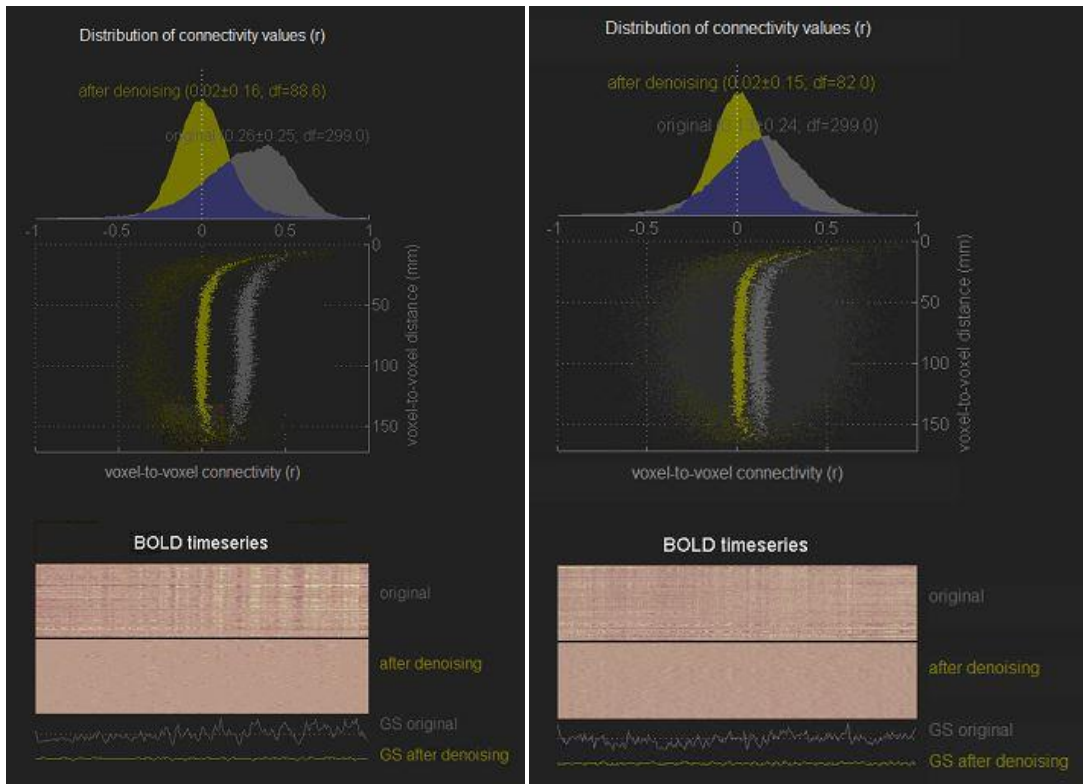
Patient 5 : Rest

Patient 5 : Music



Patient 6 : Rest

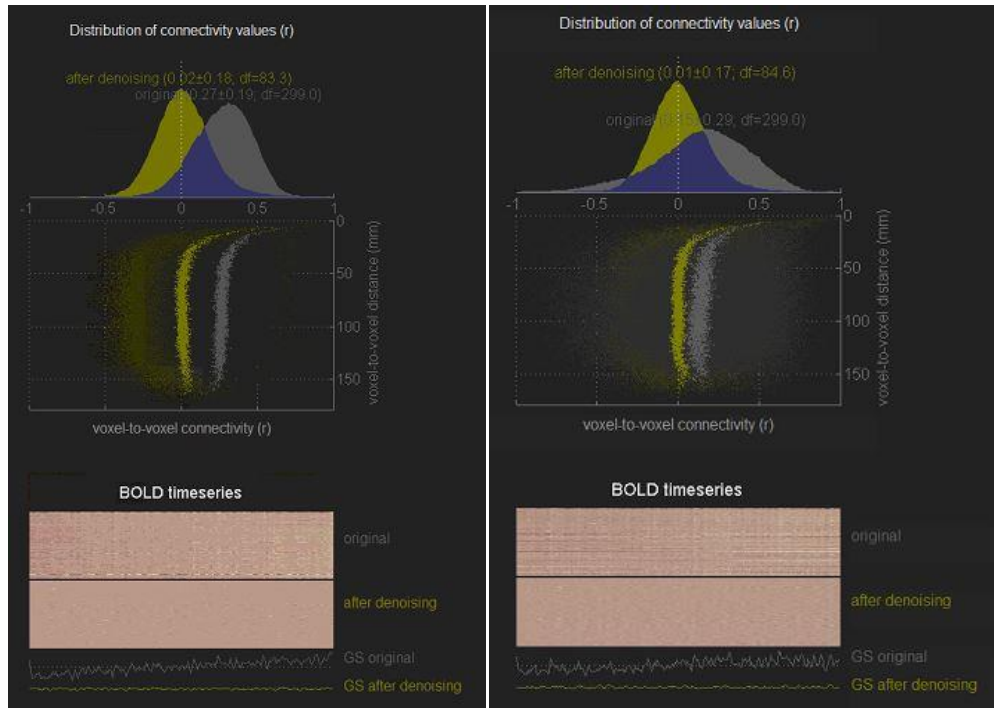
Patient 6 : Music





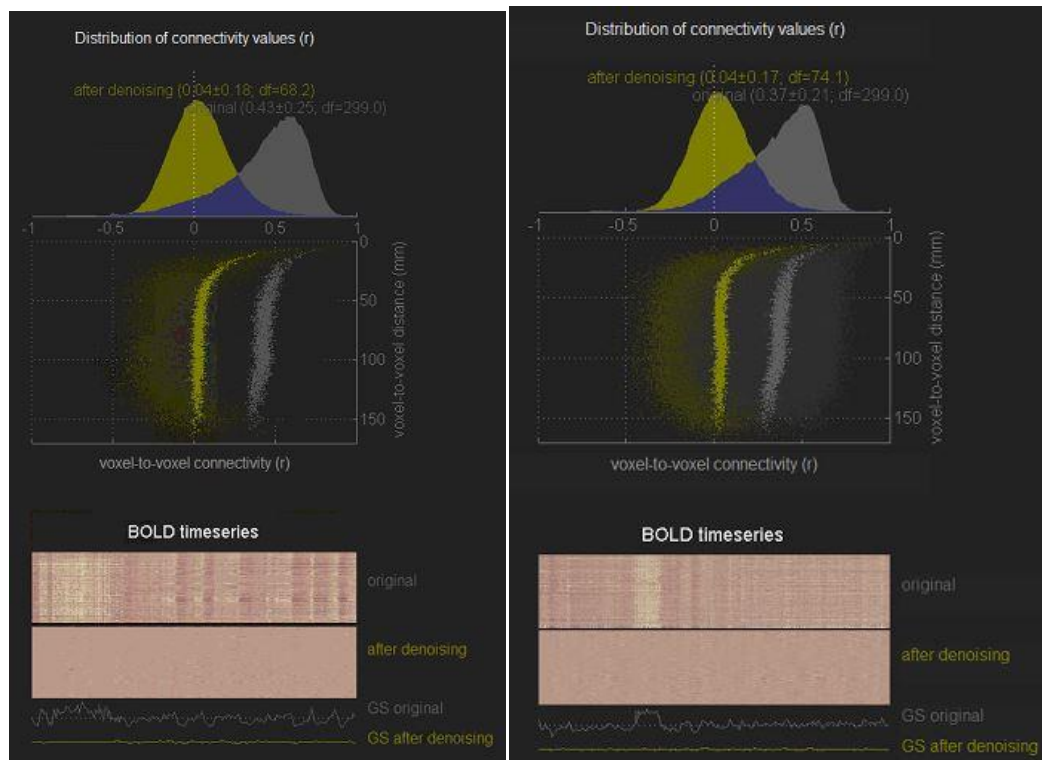
Patient 7 : Rest

Patient 7 : Music



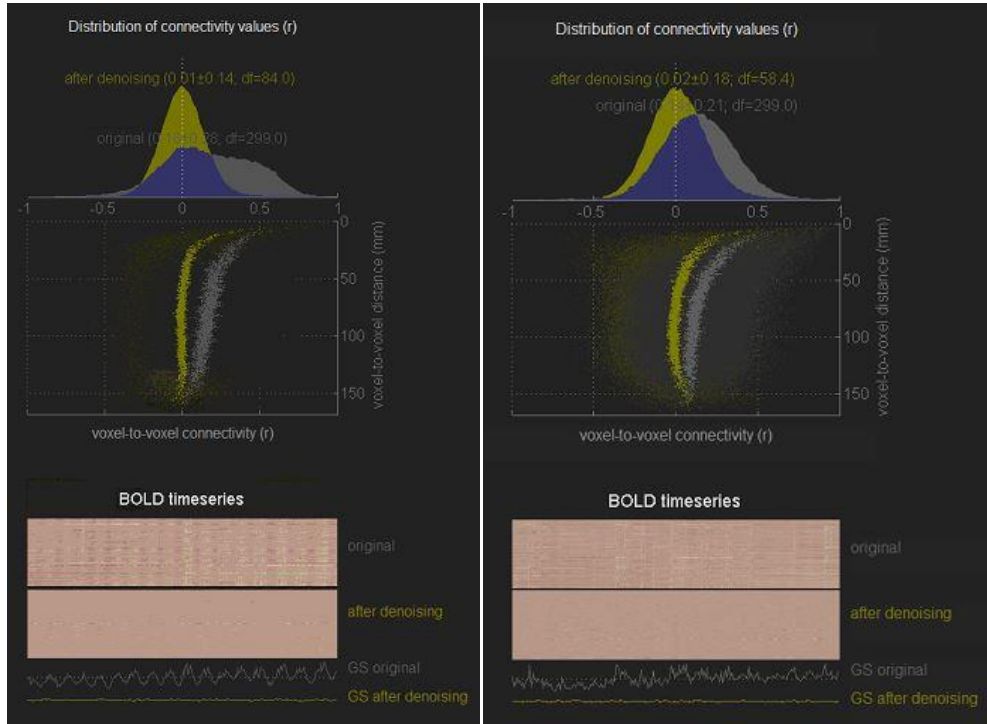
Patient 8 : Rest

Patient 8 : Music



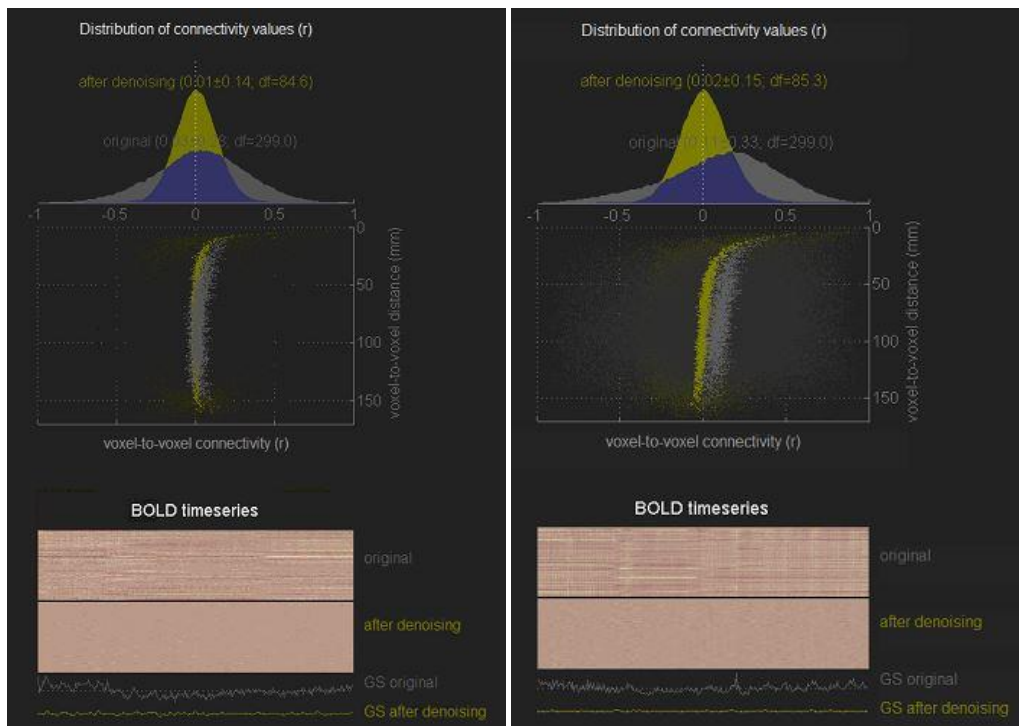
Patient 9 : Rest

Patient 9 : Music



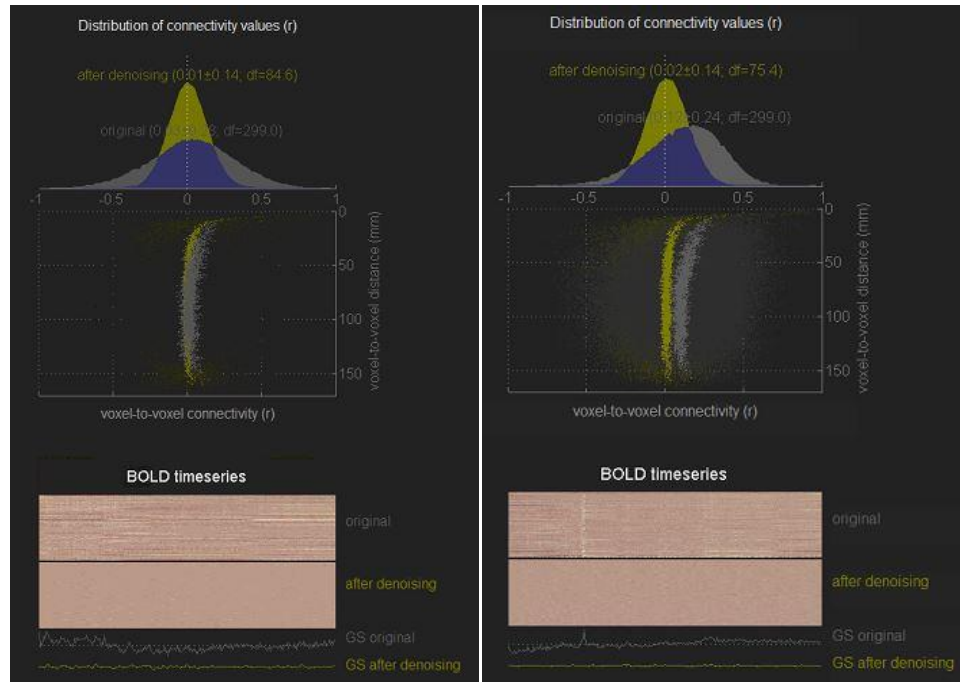
Subject 10 : Rest

Subject 10 : Music



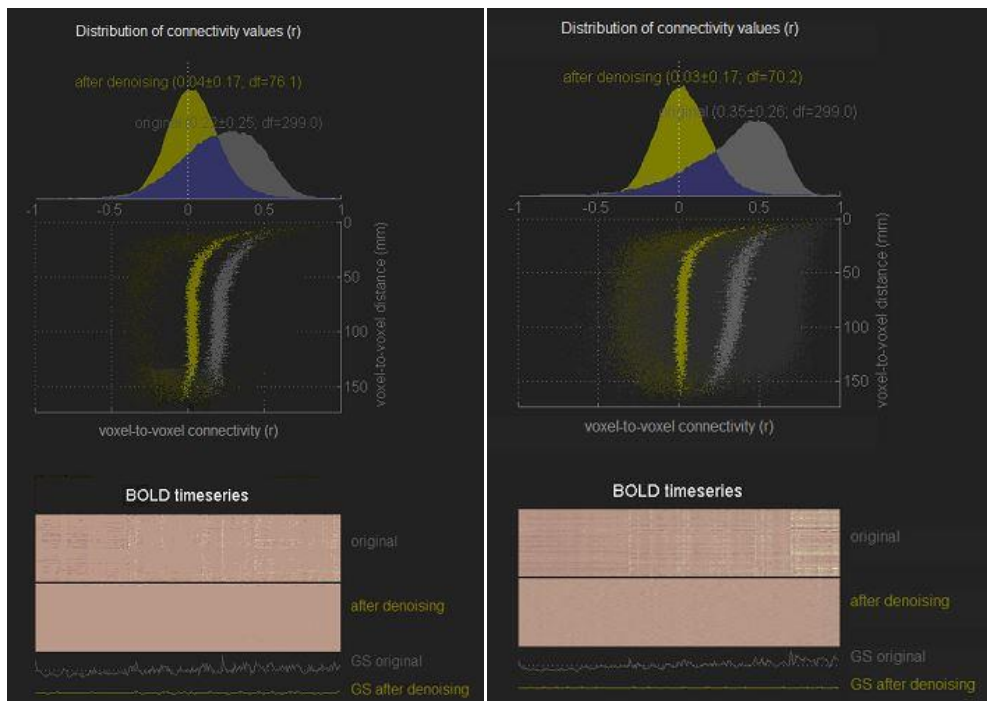
Subject 11 : Rest

Subject 11 : Music



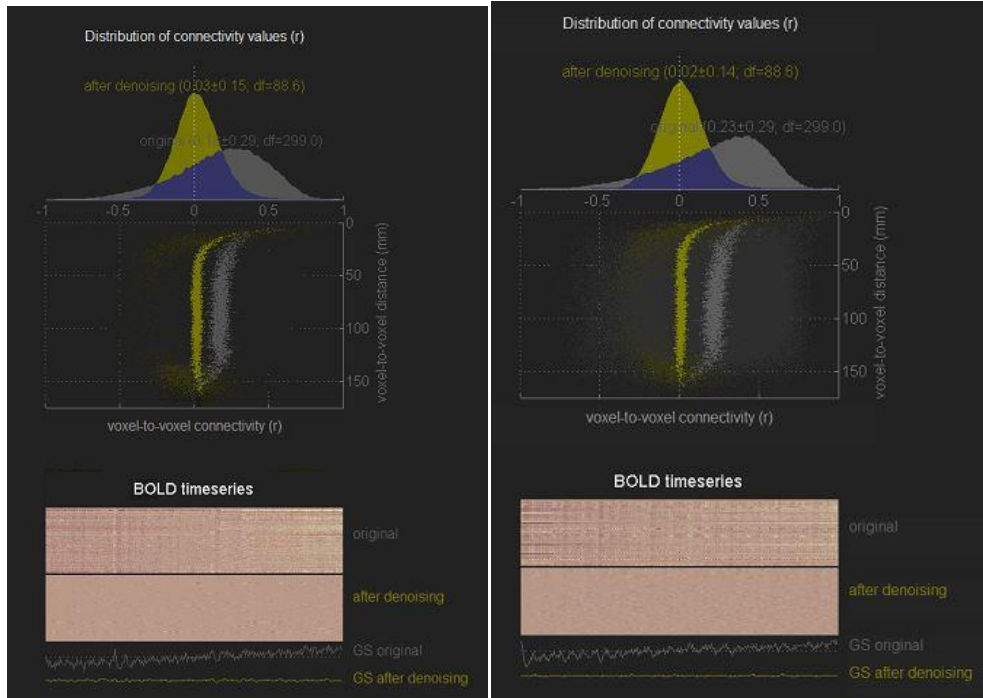
Subject 12 : Rest

Subject 12 : Music



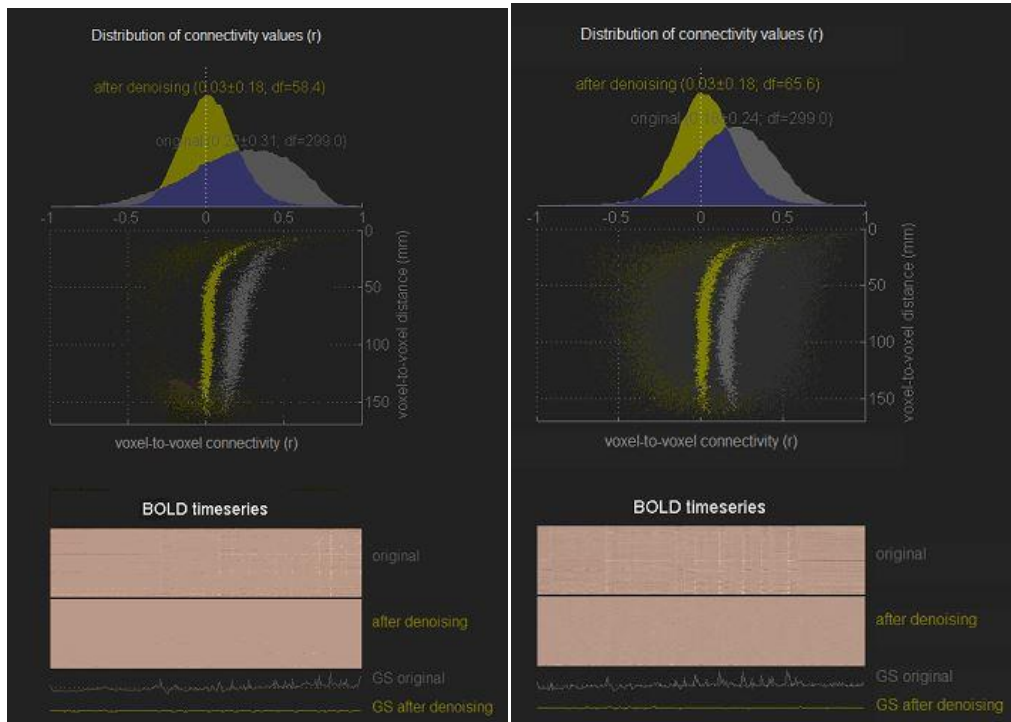
Subject 13: Rest

Subject 14: Music



Subject 14: Rest

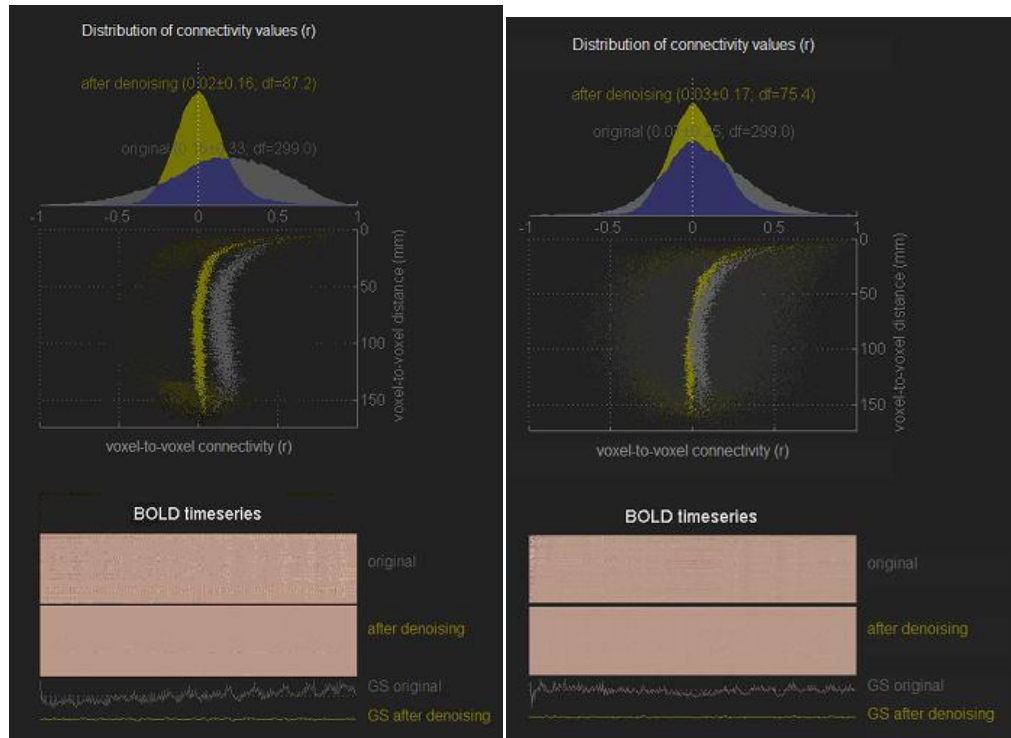
Subject 14 : Music





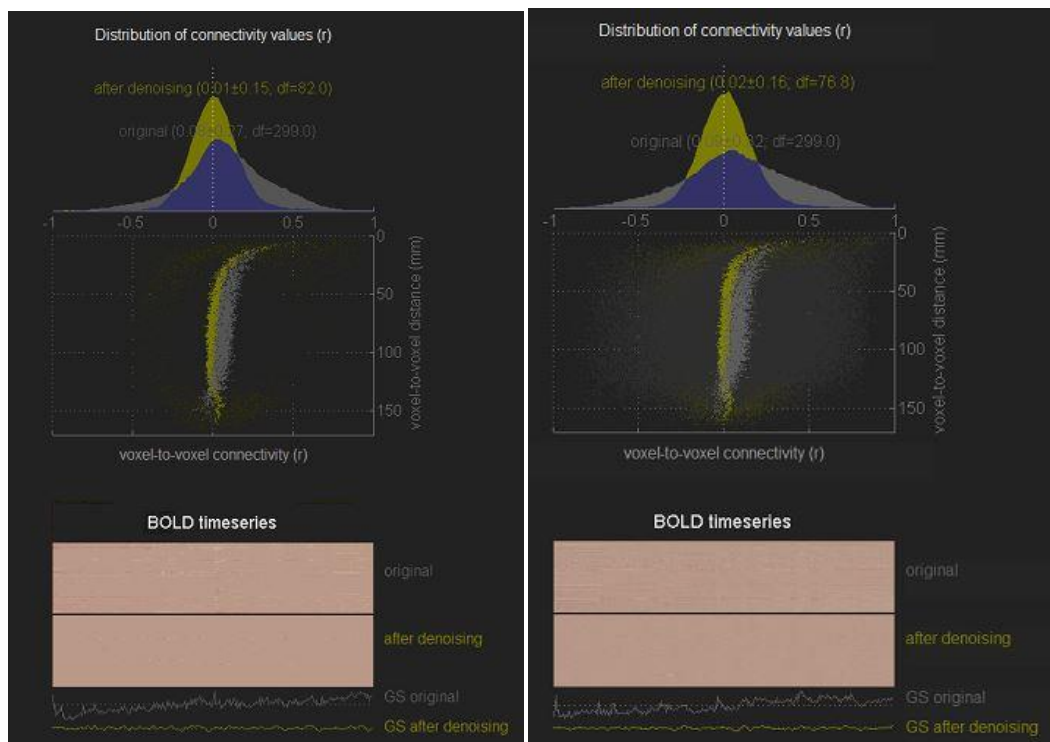
Subject 15: Rest

Subject 15 : Music



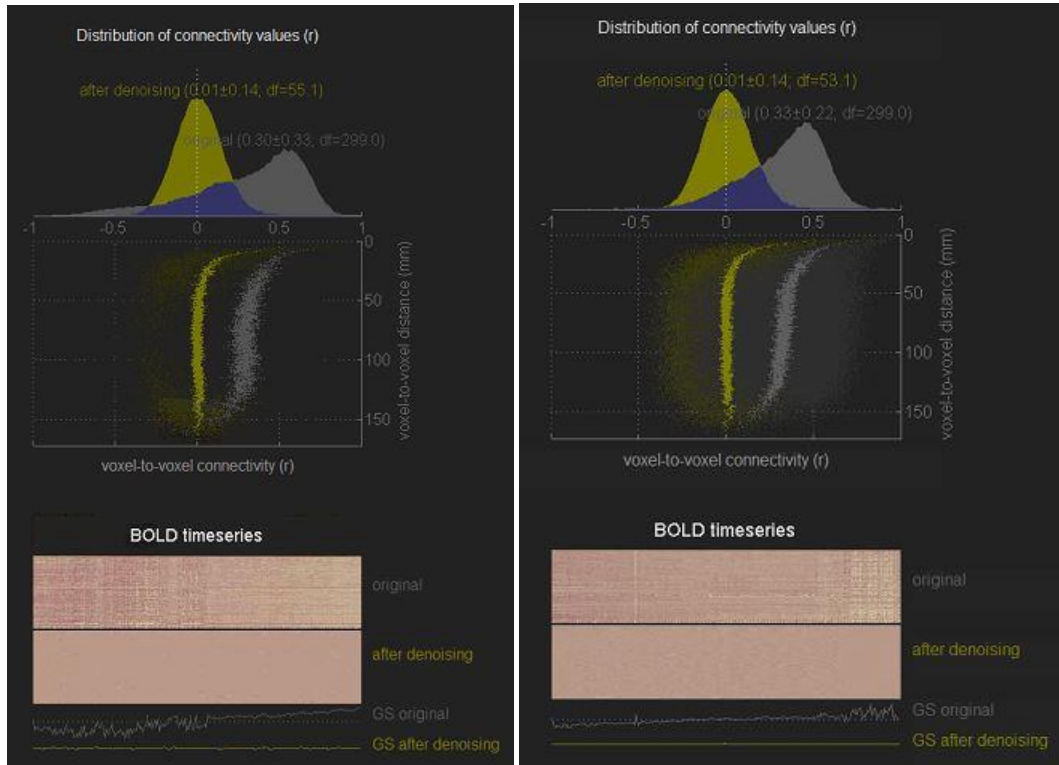
Subject 16 : Rest

Subject 16: Music



Subject 17 : Rest

Subject 17 : Music



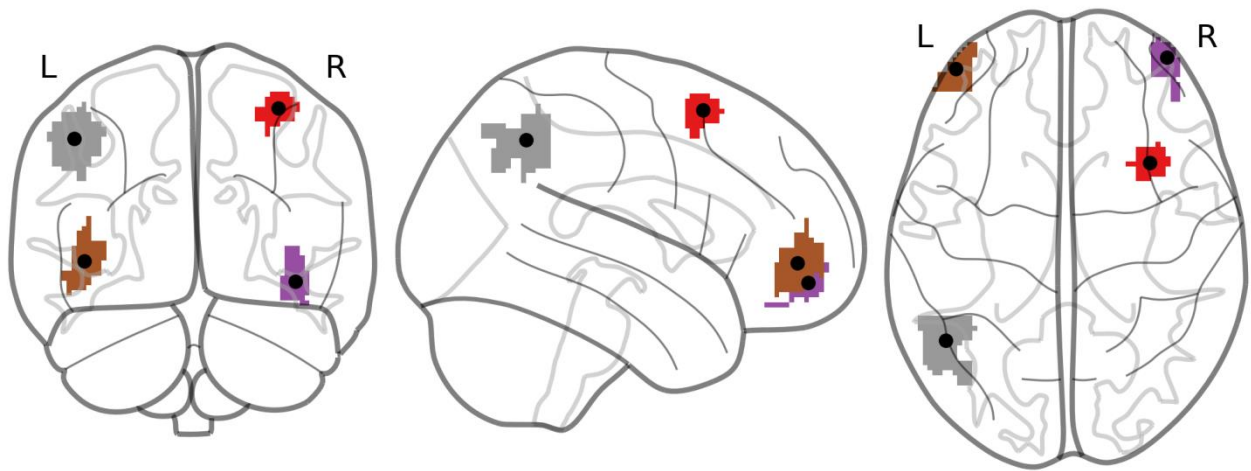
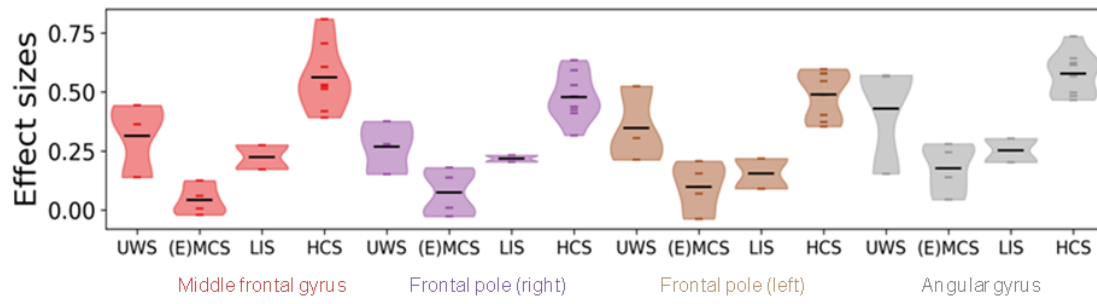
**Supplementary V.** Coordinates of all the seeds used for the network-to-voxel analyses.

<b>Networks</b>	<b>Regions</b>	<b>Coordinates</b>
<b>Default mode</b>	Posterior cingulate cortex /precuneus	1, -61, 38
	Medial prefrontal cortex	1, 55, -3
	Left lateral parietal cortex	-39, -77, 33
	Right lateral parietal cortex	47, -67, 29
<b>Frontoparietal</b>	Left lateral prefrontal cortex	-43, 33, 28
	Right lateral prefrontal cortex	41, 38, 30
	Left posterior parietal cortex	-46, -58, 49
	Right posterior parietal cortex	52, -52, 45
<b>Auditory</b>	Anterior cingulate cortex	-6, -7, 43
	Left precentral gyrus	-53, -6, 8
	Right precentral gyrus	58, -6, 11
	Left superior temporal gyrus	-44, -6, 11
	Right superior temporal gyrus	44, -6, 11
	Left visual cortex	-6, -88, 37
	Right visual cortex	6, -88, 37
<b>Music-evoked emotions</b>	Left hippocampus	-24, -16, -14
	Right hippocampus	22, -14, -14
	Left amygdala	-18, -8, -12
	Right amygdala	20, -7, -16
	Right nucleus accumbens	10, 6, 2
	Left auditory cortex	-38, -28, 14
	Right auditory cortex	48, -18, 8
	Left caudate nucleus	-8, 8, 8
	Pre-supplementary motor area	2, 16, 48
	Frontomedian cortex	8, 20, 46
	Rostral cingulate zone	2, 16, 36

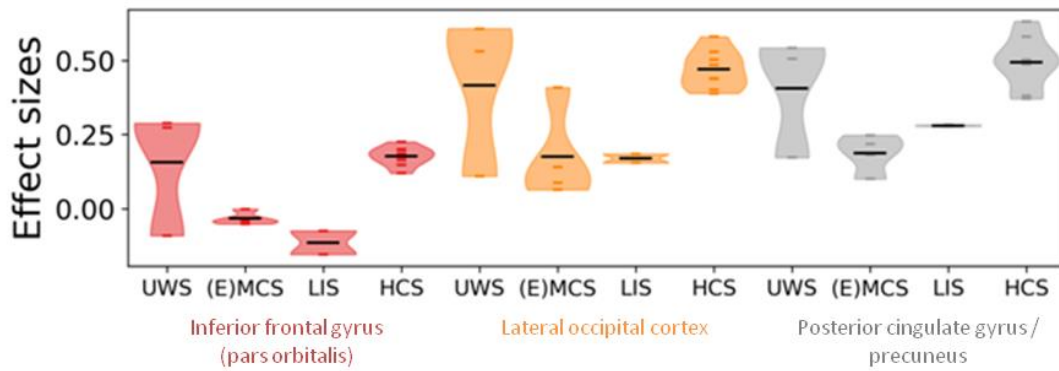
**VI. fMRI results of network-to-voxel analysis.**

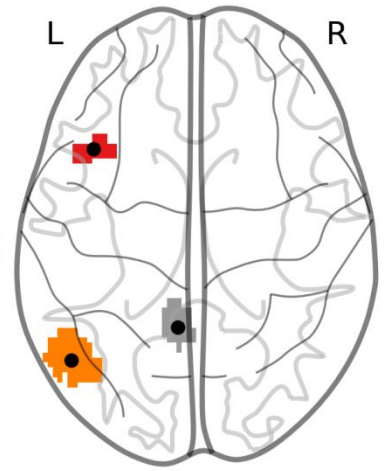
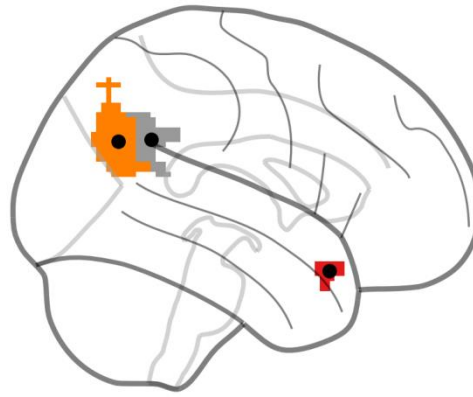
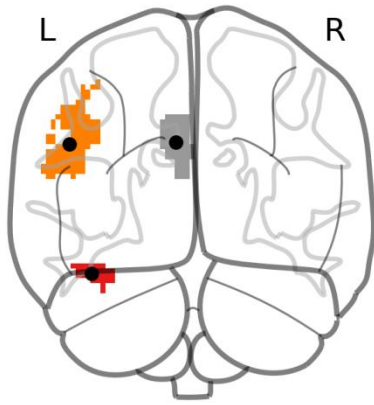
Clusters coordinates (x, y, z)			Size	Mass p-FDR	Side	Brain regions
<b>Frontoparietal network</b>						
Music condition						
-54	-60	46	568	0.000000	Left	Angular gyrus
-42	58	0	276	0.005227	Left	Frontal pole
40	16	60	207	0.006958	Right	Middle frontal gyrus
42	62	-2	146	0.013111	Right	Frontal pole
Music > rest						
0	-56	24	342	0.007634	Bilateral	Precuneus
<b>Default-mode network</b>						
Music condition						
-50	-70	40	526	0.002855	Left	Lateral occipital cortex
-8	-56	36	269	0.005887	Left	Posterior cingulate gyrus/precuneus
-36	20	-24	92	0.048416	Left	Inferior frontal gyrus (pars orbitalis)
Rest condition						
-6	-50	28	123	0.036163	Left	Posterior cingulate gyrus/precuneus
-24	-32	-14	122	0.036163	Left	Hippocampus
58	-4	-18	105	0.036163	Right	Middle temporal gyrus

**VII. Network-to-voxel analysis: fronto-parietal network (music).** The effect sizes are calculated on the overall of each cluster.

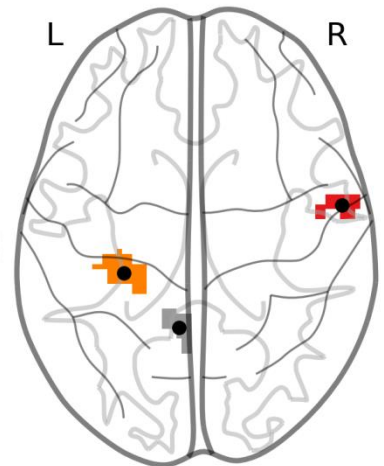
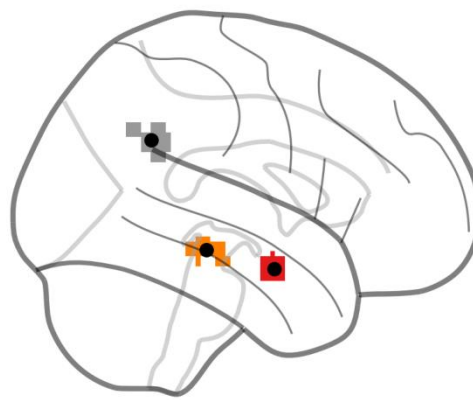
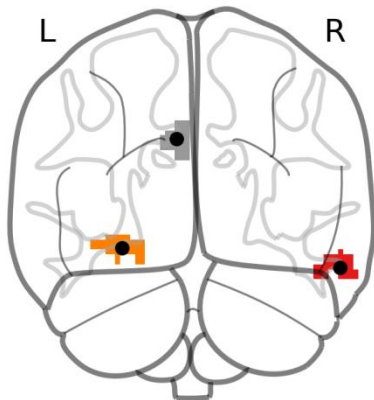
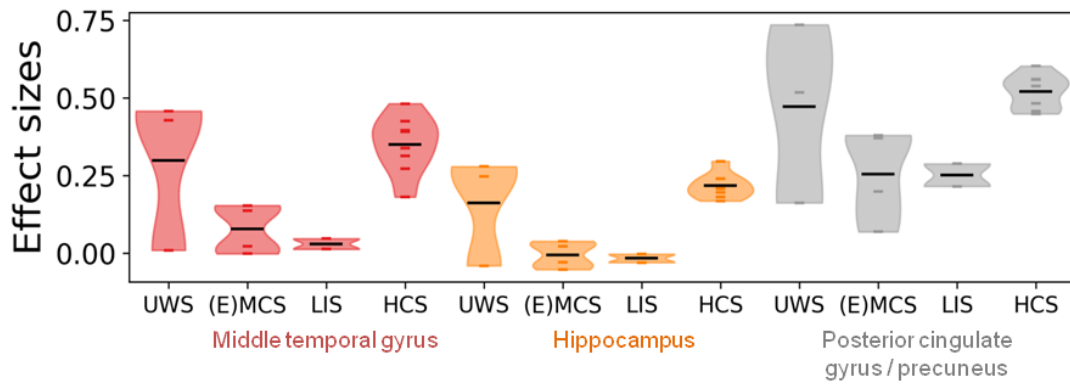


**VIII. Network-to-voxel analysis: default mode network (music).**





**IX. Network-to-voxel analysis: default mode network (rest).**



## X. fMRI results of voxel-to-voxel analysis.

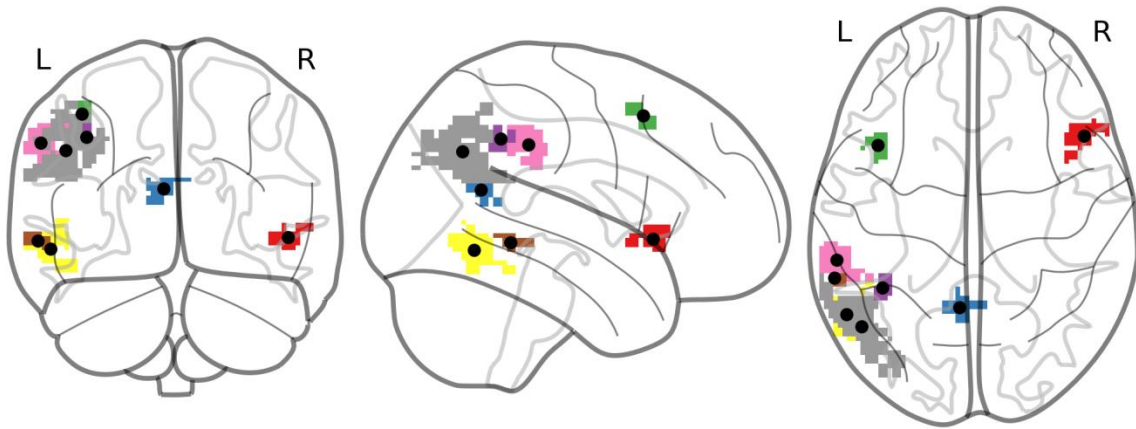
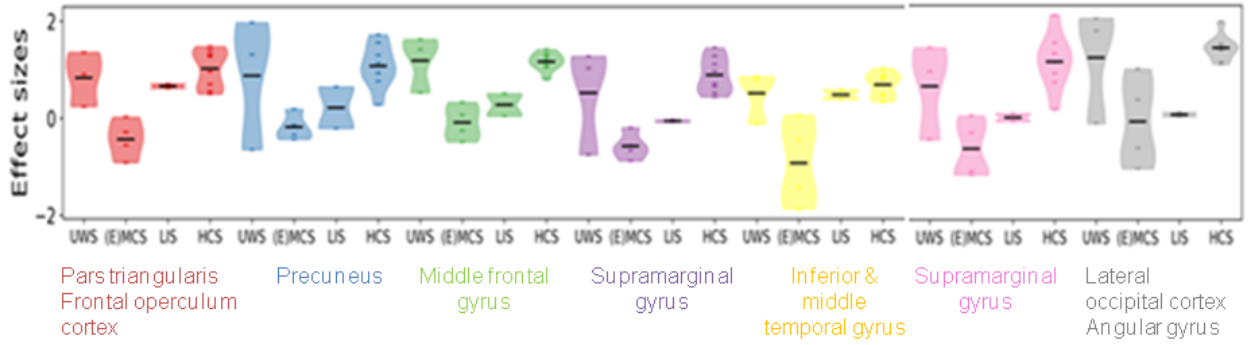
Clusters coordinates (x, y, z)			Size	Mass p-FDR	Brain regions	
<b>Intrinsic connectivity</b>						
Music condition						
-66	-52	22	654	0.001966	Left	Lateral occipital cortex Angular gyrus Supramarginal gyrus
-50	-62	-18	268	0.007649	Left	Middle & inferior temporal gyrus
-60	-32	34	198	0.008026	Left	Supramarginal gyrus
-2	-56	22	90	0.021763	Left	Precuneus
48	18	-2	113	0.016048	Right	Inferior frontal gyrus (pars triangularis) Frontal operculum cortex
-38	-50	40	63	0.039072	Left	Supramarginal gyrus
-38	16	48	52	0.040064	Left	Middle frontal gyrus
Rest condition						
-60	-62	-2	116	0.053701	Left	Middle temporal gyrus
-12	-52	4	83	0.053701	Left	Precuneus
<b>ALFF</b>						
Music condition						

0	-38	30	488	0.004176	Bilateral	Posterior cingulate gyrus
-4	-56	22	255	0.012845	Left	Precuneus
-48	44	-8	134	0.012845	Left	Frontal pole
-44	-2	-14	160	0.012845	Left	Planum polare Temporal pole
-44	-50	-18	140	0.012845	Left	Inferior temporal gyrus
-18	-20	-20	137	0.012845	Left	Parahippocampal gyrus
-62	-22	-14	90	0.025886	Left	Middle temporal gyrus
-14	-14	-30	68	0.042283	Left	Brainstem
-56	-22	-30	64	0.044898	Left	Inferior temporal gyrus
Rest condition						
-2	-50	18	198	0.039050	Left	Posterior cingulate gyrus
-50	34	16	89	0.042124	Left	Frontal pole
58	-44	34	88	0.042124	Right	Supramarginal gyrus
-50	44	-12	80	0.042124	Left	Frontal pole
Music > rest						
-12	-28	-28	218	0.006143	Left	Brainstem
-6	-46	-30	179	0.006143	Left	Vermis
34	4	-38	159	0.006143	Right	Temporal pole
22	-38	-30	156	0.006143	Right	Brainstem
-50	-38	-12	153	0.006143	Left	Inferior & middle temporal gyrus
-52	-54	32	91	0.017393	Left	Angular gyrus

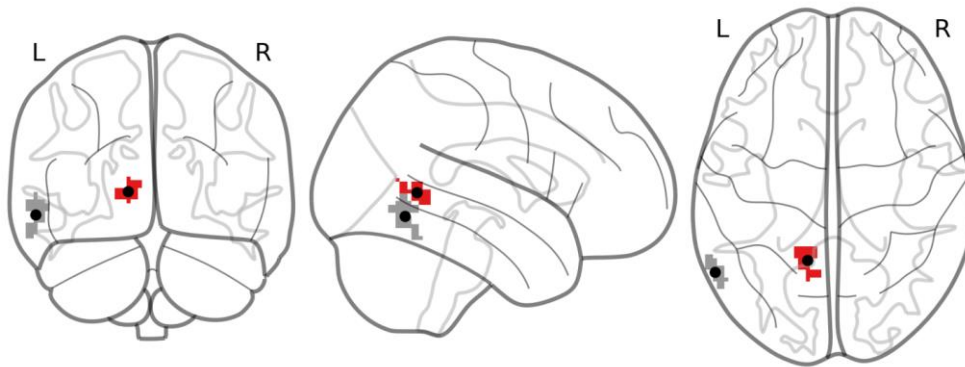
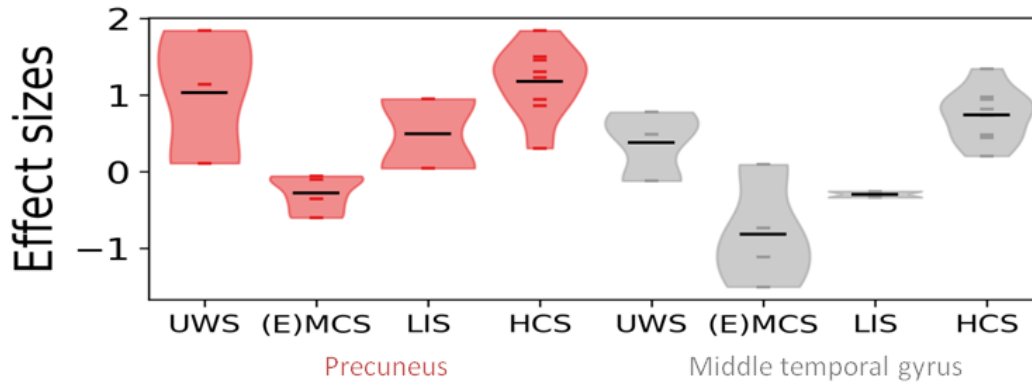


-50	-26	-24	81	0.017906	Left	Posterior inferior temporal gyrus
-38	4	-18	70	0.024860	Left	Temporal pole Insular cortex
-66	-26	-12	50	0.048830	Left	Middle temporal gyrus

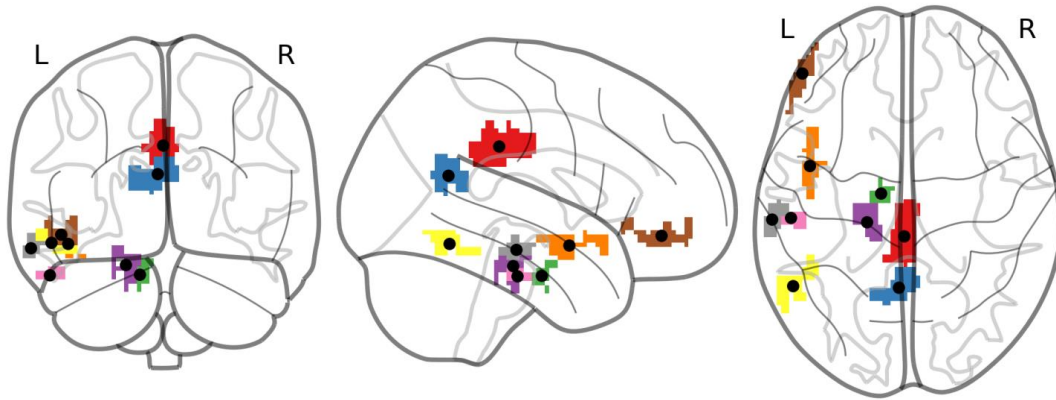
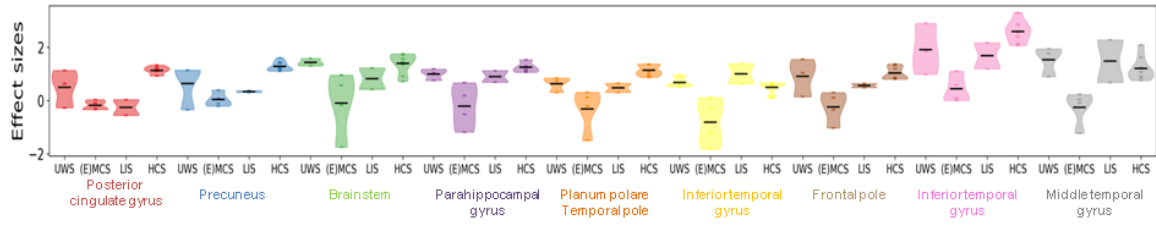
### XI. Voxel-to-voxel analysis: Intrinsic Connectivity Contrast (music).



## XII. Voxel-to-voxel analysis: Intrinsic Connectivity Contrast (rest).



### XIII. Voxel-to-voxel analysis: Amplitude of Low Frequency Fluctuation (music).



#### XIV. Voxel-to-voxel analysis: Amplitude of Low Frequency Fluctuation (rest).

