Evidence for default mode network dysfunction in borderline personality disorder

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Abstract

Background. Although executive and other cognitive deficits have been found in patients with borderline personality disorder (BPD), whether these have brain functional correlates has been little studied. This study aimed to examine patterns of task-related activation and de-activation during the performance of a working memory task in patients with the disorder.

Methods. Sixty-seven DSM-IV BPD patients and 67 healthy controls underwent fMRI during the performance of the n-back task. Linear models were used to obtain maps of within-group activations and areas of differential activation between the groups.

Results. On corrected whole-brain analysis, there were no activation differences between the BPD patients and the healthy controls during the main 2-back v. baseline contrast, but reduced activation was seen in the precentral cortex bilaterally and the left inferior parietal cortex in the 2-back v. 1-back contrast. The patients showed failure of de-activation affecting the medial frontal cortex and the precuneus, plus in other areas. The changes did not appear to be attributable to previous history of depression, which was present in nearly half the sample.

Conclusions. In this study, there was some, though limited, evidence for lateral frontal hypoactivation in BPD during the performance of an executive task. BPD also appears to be associated with failure of de-activation in key regions of the default mode network.
and 2004 (Ruocco, 2005). While some of these studies were subsequently criticised on methodological grounds (LeGris and van Reekum, 2006), more recent studies have documented circumscribed deficits in executive function and working memory (Beblo et al., 2006; Haaland et al., 2009; Hagenhoff et al., 2013). Examination of the brain functional correlates of such cognitive impairment, however, has been limited, and almost all studies to date have employed tasks with an emotional component as well. Thus, Holtmann et al. (2013) examined 16 BPD patients and 24 healthy controls using a task which required inhibition of prepotent responses in the context of either neutral or fearful faces. No areas of significant difference in activation related to cognitive performance were seen in regions of interest (ROIs) placed in the amygdala, the anterior cingulate cortex, the DLPFC and the fusiform face area. Krause-Utz et al. (2012) examined 22 BPD patients and 22 healthy controls using the Sternberg working memory task with neutral or emotional pictures as distractors. Whole-brain analysis revealed clusters of significantly different activation in the amygdala, the insula, the DLPFC and the anterior cingulate cortex among other areas. However, further examination revealed that the changes all reflected a group × emotionality interaction rather than effects related to the cognitive aspects of the task. Two studies using the go/no-go task (Silbersweig et al., 2007; Jacob et al., 2013), reviewed by Sebastian et al. (2014), failed to find evidence of activation differences in an emotionally neutral condition.

Only one study to date has used a cognitive task without an emotional component. Mensebach et al. (2009) examined 18 BPD patients during word list recall and performance of a verbal fluency task. In the former task, whole-brain analysis revealed increased activation in the patients in the posterior cingulate cortex bilaterally, the left middle and superior temporal cortex, the right lateral frontal cortex and the right angular gyrus. In the latter task, the patients again showed a pattern of increased activation, this time affecting the right posterior cingulate cortex, the right fusiform gyrus, the left anterior cingulate cortex, and the left postcentral gyrus.

Examining the brain functional correlates of cognitive task performance in BPD is also of potential interest from another perspective. This is that a number of psychiatric disorders have been described in autism (e.g. Pomarol-Clotet et al., 2008; Mannell et al., 2010; Whitfield-Gabrieli et al., 2009; Salgado-Pineda et al., 2011; Schneider et al., 2011; Dreher et al., 2012) and major affective disorder, including both major depression (Broyd et al., 2009; Grimm et al., 2009; Marchetti et al., 2012) and bipolar disorder (Pomarol-Clotet et al., 2012; Fernández-Corcuera et al., 2013). A not-dissimilar pattern of de-activation failure has also been described in autism (Kennedy and Courchesne, 2008; Spencer et al., 2012). These changes have been widely interpreted as reflecting dysfunction in the default mode network, a series of brain regions that normally de-activate during performance of tasks requiring external attention, and which include prominently two midline areas, one located anteriorly in the medial prefrontal cortex and the other posteriorly in the posterior cingulate cortex/precuneus (Buckner et al., 2008). The inferior parietal cortex, the hippocampus and the lateral temporal cortex that are also currently considered to form part of the network.

The aim in the present study was to examine brain activations in a large sample of BPD patients during performance of a cognitive, specifically executive, task. We used the n-back paradigm, which has been consistently found to produce activations in the so-called working memory network in normal subjects (Owen et al., 2005), and employed whole-brain analysis with correction for multiple comparisons. The second aim was to examine task-related de-activations, for which the n-back task is also appropriate, having been found to reliably produce de-activation in the default mode network in healthy subjects (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009; see also Piccoli et al., 2015).

Method

Participants

The patient sample consisted of 67 BPD patients (64 women and three men) who were recruited from the specialist services of two hospitals in Barcelona, the Hospital de la Santa Creu i Sant Pau and the Consorci Sanitari de l’Anoia. They were part of a total sample of 89 patients, 22 of whom were ultimately not included due to excessive movement during fMRI, poor n-back task performance or self-termination of the scanning because of claustrophobia or fatigue.

The diagnosis of BPD was made according to DSM-IV criteria, using the Spanish version of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (Villar García et al., 1995). The patients were also required to score above the cutoff (score ≥ 6) on the Spanish Revised Diagnostic Interview for Borderlines (DIB-R) (Barrachina et al., 2004). Other inclusion criteria were age between 18 and 55 years; being right-handed and having an IQ in the normal range (based on educational data plus an IQ estimate based on two subtests of the WAIS-III, Vocabulary and Matrix Reasoning).

Fifty of the 67 patients were taking psychotropic medication: 24 antidepressants (13 with a mood stabiliser as well), four antipsychotics (1 with a mood stabiliser as well); and 16 both antidepressants and antipsychotics (four with a mood stabiliser). Six patients were on mood stabilisers only.

Exclusion criteria were: history of brain trauma (as indexed by skull fracture, loss of consciousness for more than 24 h or presence of post-traumatic amnesia), presence of neurological disease and alcohol/substance abuse or dependence within the 6 months prior to participation. Any patients who had a history of schizophrenia, schizoaffective disorder or bipolar affective disorder, as assessed using the lifetime version of the Structured Clinical Interview for DSM-IV (SCID-I) (First, 1999), were also excluded. Because major depression is itself associated with brain functional changes (e.g. Drevets, 2000; Rive et al., 2013), we excluded patients who currently met criteria for major depression. However, we did not exclude patients who had previously met criteria for this disorder, but instead examined its potential influence on any brain functional changes found.

A sample of healthy control subjects was recruited from non-medical staff working in the above two and other hospitals, their relatives and acquaintances, and independent sources in the community. The controls were recruited to be similar to the patient sample in terms of age, sex and estimated IQ. They were interviewed and excluded if they reported a history of mental illness or treatment with psychotropic medication. They were also questioned about family history of mental illness and excluded if a first-degree relative had experienced symptoms consistent with a major psychiatric disorder.
**fmri task**

The participants performed a sequential-letter version of the n-back task (Gevins and Cutillo, 1993). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner. Each block consisted of 24 letters that were shown every 2 s (1 s on, 1 s off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. Four 1-back and four 2-back blocks were presented in an interleaved way, and between then a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 s. To identify which task had to be performed, characters were shown in green in 1-back blocks and in red in the 2-back blocks. All participants went through a training session outside the scanner. The n-back task was programmed using the Tcl-Tk language.

The behavioural measure used was the signal detection theory index of sensitivity, d′ (Green and Swets, 1966). Higher values of d′ indicate better ability to discriminate between targets and distractors. Subjects who had negative d′ values in either or both of the 1-back and 2-back versions of the task, which suggests that they were not performing it, were excluded from the study.

**fmri data acquisition**

In each scanning session, 266 volumes were acquired from a 1.5-T GE Signa scanner. A gradient-echo echo-planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 40 ms, flsc angle = 70°, section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3×3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

**fmri data analysis**

fmri image analyses were performed with the FEAT module, included in FSL software (Beckmann et al., 2006). At a first level, images were corrected for movement and eventually co-registered to a common stereotaxic space (Montreal Neurologic Institute template). To minimise unwanted movement-related effects, individuals with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study and thus are not reported. General linear models (GLMs) were fitted to generate individual activation maps for the 1-back and 2-back tasks v. baseline and also the 2-back v. 1-back contrast.

Comparisons between groups were made to evaluate differences between BPD and healthy controls. These comparisons were performed within the FEAT module, fitting mixed-effects GLM models (Beckmann et al., 2006) and thresholding the results at the cluster level at a corrected p-value of 0.05.

Additionally, a functional connectivity analysis was performed to evaluate potential differences in the default mode network integrity between patients and controls while performing the n-back task. Specifically, the pipeline proposed by the FSL group based on combining a probabilistic independent component analysis (Melodic ICA) followed by a two-step dual regression (Nickerson et al., 2017) on the default mode network component was applied to our data.

**Results**

**Demographic and clinical data**

Demographic data on the patients and controls are shown in Table 1. The two groups were well matched for age, sex and estimated IQ.

Thirty-one of the BPD patients had a history of major depression and 36 did not. These two subgroups did not differ significantly in age (with depression: mean 32.77 ± 6.73 years; without depression: mean 31 ± 7.29 years; t = 1.05; p = 0.3); sex (with depression: 30 women and 1 man; without depression: 34 women and 2 men; χ² = 0.21; p = 0.65); and IQ (with depression: mean 96.30 ± 14.70; without depression: mean 97.62 ± 17.13; t = 0.33; p = 0.74).

**Behavioural performance**

The patients and the controls did not differ significantly on the 1-back version of the task (mean d′ controls: 4.31 ± 0.73; mean d′ patients: 4.20 ± 0.77; t = 0.89, p = 0.37) or on the 2-back version (mean d′ controls: 3.26 ± 0.91; mean d′ patients: 3.02 ± 0.94; t = 1.54, p = 0.12).

**Within-group activations and de-activations and comparison between groups**

The main focus here was on the 2-back v. baseline contrast, but for completeness we also report findings for the 2-back v. 1-back contrast. Activations in the 1-back v. baseline contrast were broadly similar to but less extensive than those in the 2-back v. baseline contrast and are not described further (for details of this analysis see online Supplementary text and Supplementary Fig. 1).

2-Back v. baseline: In this contrast the healthy controls showed a large confluent cluster of significant activation in the DLPFC bilaterally and the superior medial prefrontal cortex, extending bilaterally to temporal and occipital regions, posterior parietal areas, and subcortically to the putamen, the pallidum and the thalamus (77 688 voxels, peak at x = −34, y = −52, z = 12.1; p < 0.001) (see Fig. 1a). The same cluster involved parts of the left and right insula, neighbouring regions of the frontal operculum and the cerebellum. There was also a single large cluster of de-activation (70 826 voxels, peak at x = −2, y = 50, z = 11.2; p < 0.001). It extended from the medial frontal region to the superior occipital cortex and included the anterior and posterior cingulate gyrus, as well as the precuneus/uneus and parts of the lingual gyrus and fusiform gyrus. This cluster also included the temporal poles extending to the superior temporal cortex and the supramarginal/inferior parietal cortex, and also the bilateral amygdala, hippocampus and parahippocampal regions.
The pattern of activations in the BPD patients was broadly similar to that in the healthy controls (see Fig. 1b). A large cluster of 86,332 voxels (peak at: \(-34 20 2; z = 11.3; p < 0.001\)) was located in the DLPFC, the occipital region and the temporal and parietal cortex. Unlike the controls, however, the patients also showed activation in the head of the caudate nucleus bilaterally. De-activations were seen in a large cluster of 39,751 voxels (peak at: \(-2 -50 32; z = 10.3; p < 0.0001\)) that encompassed the medial frontal region and the anterior and posterior cingulate gyrus, also involving the superior occipital cortex, the posterior insular cortex, the precuneus/cuneus, and lingual, fusiform and parahippocampal regions.

In the between group comparison, there were no clusters where the patients showed reduced activation relative to the healthy controls. However, the patients showed two clusters of relatively increased activation (see Fig. 1c). One (18,566 voxels; peak at: 0 46 14; \(z = 9.89; p = 3.21 \times 10^{-38}\)) was located in the medial prefrontal cortex and the orbitofrontal cortex, extending to the right pre- and postcentral cortex, the posterior insula and superior temporal cortex bilaterally, and the amygdala, the anterior hippocampus and the parahippocampal area. A second cluster was in the cuneus and lingual area bilaterally (2168 voxels; peak at: \(-6 -56 12; z = 6.63; p = 2.8 \times 10^{-6}\)). The third was in the left pre/postcentral cortex (1039 voxels; peak at: \(-36 -32 68; z = 7.3; p = 0.002\)) and the fourth (662 voxels; peak at: \(-20 -100 16; z = 6.64; p = 0.03\)) and fifth (595 voxels; peak at: \(-22 -102 18; z = 5.3; p = 0.048\)) were in the right and left superior occipital cortex, respectively.

Because the first cluster of significant difference between the BPD patients and the healthy controls was large and extended subcortically to the amygdala, hippocampus and caudate nucleus, ROIs for these subcortical regions were also extracted and examined separately, using the MNI standard atlas provided in the FSL package. Boxplots for these regions are shown in Fig. 2; it can be seen that the changes in the amygdala and hippocampus represented diminished de-activation in the patients, whereas the caudate nucleus was activated in the patients but not in the controls.

**2-Back v. 1-back:** Activations and de-activations for the healthy controls and the BPD patients in this contrast are shown in Fig. 3a and b. As in the 2-back v. baseline contrast the controls showed a large bilateral confluent cluster of significant activation (115,980 voxels; peak at: \(-34 -66 -36; z = 11.3; p < 0.001\)) that included the DLPFC and the superior middle and medial prefrontal cortex, the left and right insula, regions of the temporal, occipital and parietal cortex and the putamen, pallidum, thalamus and posterior hippocampus. This cluster also involved the cerebellum. Five clusters of de-activation were also seen: one (26,820 voxels; peak at: 0 46 14; \(z = 9.89; p = 3.21 \times 10^{-38}\)) was located in the medial prefrontal cortex and the orbitofrontal cortex, extending to the right pre- and postcentral cortex, the posterior insula and superior temporal cortex bilaterally, and the amygdala, the anterior hippocampus and the parahippocampal area. A second cluster was in the cuneus and lingual area bilaterally (2168 voxels; peak at: \(-6 -56 12; z = 6.63; p = 2.8 \times 10^{-6}\)). The third was in the left pre/postcentral cortex (1039 voxels; peak at: \(-36 -32 68; z = 7.3; p = 0.002\)) and the fourth (662 voxels; peak at: \(-20 -100 16; z = 6.64; p = 0.03\)) and fifth (595 voxels; peak at: \(-22 -102 18; z = 5.3; p = 0.048\)) were in the right and left superior occipital cortex, respectively.

The pattern of activations in the BPD patients was again similar to that in the healthy controls. There was a large cluster (96,329 voxels; peak at: 4 20 48; \(z = 9.66; p < 0.001\)) extending from the DLPFC to occipital regions and including the temporal and parietal cortex and the head of the caudate nucleus bilaterally.
De-activations were seen in four clusters. One (10,898 voxels; peak at $0.30 - 6.00.30 - 6$; $z = 6.22$; $p = 1.73 \times 10^{-20}$) was located bilaterally in the medial prefrontal and orbitofrontal cortex extending to the posterior insula and rolandic operculum, as well as to the amygdala, anterior hippocampus and parahippocampal area. A second cluster (1,523 voxels; peak at $-8.52 - 62.52 - 62$; $z = 5.27$; $p = 9.72 \times 10^{-5}$) involved the calcarine cortex, the cuneus and the precuneus. A third cluster was in the right pre/postcentral cortex (1,486 voxels; peak at $42.42 - 28 70; 42.42 - 28 70; z = 3.92; p = 0.0001$). Finally, a cluster (648 voxels; peak at $-10.64 - 104 10; -10.64 - 104 10; z = 3.75; p = 0.03$) was seen in the left occipital cortex.

In the 2-back v. 1-back contrast, unlike the 2-back v. baseline contrast, the BPD patients showed clusters of reduced activation compared to the healthy controls (see Fig. 3c). One was a bilateral cluster in the cerebellar vermis (1,256 voxels; peak at $12.12 - 62 - 38; 12.12 - 62 - 38; z = 4.29, p = 0.0005$). The second and third clusters were in the left (1,249 voxels; peak at $-36.12 - 32; -36.12 - 32; z = 4.14; p = 0.0005$) and right (1,045 voxels; peak at $22.22 - 6 44; 22.22 - 6 44; z = 4.23; p = 0.002$) precentral cortex. Finally, there was a cluster in the left parietal cortex (617 voxels; peak at $-54.61 - 48 62; -54.61 - 48 62; z = 4.14; p = 0.04$).

There were two clusters of relative de-activation in the patients. One was in the medial frontal cortex bilaterally, mainly localised...
subgenually and perigenually (9140 voxels; peak at $0.44 - 18; z = 4.78; p = 4.21 \times 10^{-18}$). This cluster also extended subcortically to involve the left hippocampus and amygdala. The other cluster was in the right inferior temporal cortex (2601 voxels; peak at $46 16 - 42; z = 4.45; p = 2.98 \times 10^{-7}$). It also extended subcortically to involve the right hippocampus and amygdala.

Functional connectivity findings

The combined Melodic ICA+ dual regression analysis findings for the healthy controls and BPD patients are shown in online Supplementary Material (Fig. S3). Comparison between the two groups revealed no significant differences in the functional connectivity of the default mode network.

Relationship to history of major depression

To investigate the influence of this variable, mean activations in the BPD patients with and without a history of major depression were examined in ROIs based on the clusters that emerged in the comparison between the BPD patients and the healthy controls.

In the 2-back vs. baseline contrast there was a trend towards greater de-activation in one of the two clusters of de-activation (cluster 1, inferior medial frontal cortex/temporal cortex/hippocampus/parahippocampal gyrus) in the patients with a history of depression (with depression: mean $-6.8 \pm 8.38$; without depression: mean $-2.9 \pm 9.61; t = 1.73, p = 0.09$) (see Fig. 4). Findings were in the same direction in the second cluster (cluster 2, precuneus/calcarine cortex), but did not reach trend level (with depression: mean $-5.36 \pm 5.83$; without depression: mean $-3.95 \pm 7.27; t = 1.47, p = 0.16$).

ROIs based on the six clusters that emerged in the comparison between the BPD patients and the controls in the 2-back vs. 1-back contrast were also compared between patients with and without a lifetime history of major depression. No significant differences were found (see online Supplementary Table S1).

Discussion

The major finding of this study was that patients with BPD showed a pattern of failure of de-activation in the two midline regions of the default mode network, along with other regions including the bilateral temporal cortex and the hippocampus. We also found evidence of reduced working memory-related activation in the patients in the precentral gyrus and the left inferior parietal cortex, although these changes were only present in the 2-back vs. 1-back contrast. None of the changes found appeared to be attributable to lifetime history of depression, which was present in nearly half the sample.

The fact that the BPD patients in our study did not show any evidence of reduced task-related activation in the main 2-back vs. baseline comparison is perhaps understandable, given that they did not show poorer performance on the task than the healthy controls. On the other hand, we did find evidence of reduced activation in the 2-back vs. 1-back contrast: this affected the left parietal cortex, which is part of the working memory network (Owen et al., 2005), though not the DLPFC. As noted in the Introduction, imaging studies that have examined cognition-related (as opposed to emotion-related) brain activations in BPD have had variable findings, either of no differences from controls (Silbersweig et al., 2007; Krause-Utz et al., 2012; Holtmann et al., 2013) or increased activation (Mensebach...
et al., 2009). Taken together, therefore, the findings to date concerning cognitive task-related activation alterations in BPD remain equivocal.

The possibility that BPD is characterised by failure of de-activation has not previously attracted attention. In the only other study that reported de-activations, Minzenberg et al. (2007) examined 12 BPD patients and 12 healthy controls while they viewed fearful, angry and neutral faces. In the comparison between fearful and neutral faces, they found that the patients showed increased de-activation in the anterior cingulate cortex, i.e. the opposite of what we found. However, it may also be relevant here that Schulze et al.’s (2016) meta-analysis of studies of emotional and cognitive-emotional tasks in BPD found evidence for increased activation in the posterior cingulate gyrus. Since the subtractive nature of fMRI analysis means that greater activation and reduced de-activation will both produce a picture of apparent hyperactivation (see Gusnard and Raichle, 2001), it is possible that this apparent increased activation may actually have represented failure of de-activation.

We also found failure of de-activation in the hippocampus and amygdala, bilaterally in the 2-back v. baseline contrast and on the left in the 2-back v. 1-back contrast. The hippocampus is currently considered to form part of the default mode network, and so this finding is not unexpected. However, the amygdala does not form part of the network, although Price and Drevets (2012) have noted that it has close connections with the medial frontal cortex, and argued that it forms part of an extended system which is involved in forebrain modulation of visceral function in response to sensory or emotive stimuli. Our findings with respect to these subcortical structures are additionally of interest because they have been found to show structural abnormality in BPD.

Thus, two meta-analyses of studies examining ROIs in the amygdala and/or hippocampus found evidence for volume reductions in BPD (Nunes et al., 2009; Ruocco et al., 2012). Schulze et al. (2016) also found reduced volume of the right hippocampus, and less robustly of the left hippocampus, in a meta-analysis of 10 whole-brain, voxel-based studies of BPD.

Abnormalities in the default mode network have also been found at rest in BPD. Thus, Visintin et al. (2016) pooled data from three studies that examined resting-state activity using PET in patients with the disorder and found evidence for it being increased in the medial prefrontal cortex and the right precuneus/posterior cingulate cortex, although with significant heterogeneity. Four studies using fMRI to examine resting-state connectivity have further supported these findings (Salvador et al., 2014; Xu et al., 2016; Baczkowski et al., 2017; Lei et al., 2017). Our functional connectivity analysis did not reveal evidence of abnormality in the default mode network in BPD patients. However, it should be noted that this was not specifically a resting-state connectivity analysis.

The question arises of what default mode network dysfunction in BPD might imply. Clues to the normal function of the network come from the fact that, while most cognitive tasks produce de-activation in healthy subjects, some been found to activate parts of it (see Buckner et al., 2008). These tasks include autobiographical recall (Svoboda et al., 2006), imagining the future (Schacter et al., 2007), making social and emotional judgements about oneself (and others) (Murray et al., 2012), making moral judgments (Boccia et al., 2017) and performing some theory of mind tasks (Schurz et al., 2014). This has led to the view that the default mode network is particularly concerned with self-related mental activity (Buckner et al., 2008), or making mental simulations of the world (Buckner, 2012), both of which are of obvious relevance to psychiatric disorders such as schizophrenia and autism. Such a conceptualisation might also be applicable to some aspects of BPD, for example identity disturbance, but seems less easy to apply to other aspects of the disorder, especially the emotional dysregulation that is a prominent part of its symptomatology – although the close connections between the medial frontal cortex and the amygdala noted by Price and Drevets (2012), above, could be important for this.

In conclusion, our findings suggest that it might be appropriate to add BPD to the growing list of psychiatric disorders – including schizophrenia, major affective disorder and autism – that are characterised by default mode network dysfunction. Some limitations need to be acknowledged. Although the sample was large by functional imaging standards, at 31 and 36, the numbers in the subsamples with and without a history of major depression may not have been sufficient to detect differences between them. We did not examine for relationships with other comorbidities of BPD such as post-traumatic stress disorder and psychotic-like experiences. Given that the majority (50 of 67) of the BPD patients were taking a variety of different psychotropic medications, it was not possible to examine whether there were associations between medication status and the functional imaging changes found. Finally, the study was carried out using...
a 1.5T scanner, which is less sensitive than the increasingly used 3T imaging.

**Supplementary material.** The supplementary material for this article can be found at [https://doi.org/10.1017/S0033291719001880](https://doi.org/10.1017/S0033291719001880)

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**Conflict of interest.** None declared.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals. The study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the relevant research ethics committee (Comité Ético de Investigación Clínica de las Hermanas Hospitalarias, Barcelona). Written informed consent was obtained from all subjects. The participants did not receive any economic compensation.

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