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RESEARCH ARTICLE

The Neurobiological Basis of the Distress Thermometer: A PET Study in Cancer Patients

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Abstract

The objective of this study was to investigate the possible associations between the Distress Thermometer (DT) scores and the brain metabolism of structures involved in stress response. Twenty-one cancer patients were assessed using the DT, Problem Checklist and Hospital Anxiety and Depression Scale (HADS). The psychological measures were correlated with [18 F]PET-FDG brain glucose metabolism. Multiple and linear regression and binary logistic regression were run to analyse data.

The DT and HADS scores illustrated that 48% of patients were distressed, 19% were depressed and48% were anxious. Results showed that some subcortical areas activity, such as part of midbrain and of hypothalamus, was correlated with the DT scores. The Problem Checklist scores correlated with the activity of the same areas and included more regions in the limbic forebrain and brainstem.

Compared with the DT and Problem Checklist, HADS-Depression scores showed a more extensive pattern of correlation with brain activity, including limbic and cortical areas.

The results highlighted that the DT scores correlated with the activity of brain areas typically involved in stress response. Indeed, hypothalamus metabolism was found to be the best predictor of distressed patients.

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Keywords

distress thermometer; cancer; brain metabolism; depression; [18 F]FDG PET

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Introduction

According to the National Comprehensive Cancer Network (NCCN) panel, an alliance of 21 cancer

centres in the United States, working within the clinical practice guidelines for distress management, distress is 'a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation and existential and spiritual crisis (2013, p.2).' Distress is a common problem that affects 30–40% of cancer patients during all the phases of disease trajectory.

In order to rapidly detect distress, the NCCN panel developed the Distress Thermometer (DT), a short screening tool (Holland, 1997) that is an integral part of the NCCN Clinical Practice Guidelines for distress management (www.nccn.org), with the last edition issued in 2013 (Kvale, Murthy, Taylor, Lee, & Nabors, 2009; NCCN, 2013). Because of its conciseness and suitability both for patients and clinicians to easily identify emotional distress, the DT has become, over the last 15 years, one of the most used tools widely applied in mixed oncology settings to screen cancer

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patients both in early (Hegel et al., 2008) and advanced (Ryan, Gallagher, Wright, & Cassidy, 2012) stages of the disease.

The DT has been shown to be a sensitive and specific tool in order to evaluate distress in cancer. In a multicenter study, it was demonstrated that, compared with psychological tools used as gold-standard reference instruments [such as the Hospital Anxiety and Depression Scale (HADS) and the Brief Symptom Inventory-18], a DT cut-off of 4 optimized sensitivity and specificity for the detection of patients with psychological distress (Jacobsen et al., 2005). This result was confirmed by other studies and by a recent study carried out in Italy (Grassi et al., 2013).

The DT is one of the first-step screening tools to detect patients to be further investigated bymeans of more specific scales or in-depth interviews (Hegel et al., 2008, 2006; Lynch, Goodhart, Saunders, & O'Connor, 2010). This procedure avoids an excessive burden on both patients and clinicians and allows clinicians to manage patients and to orient themto psychological and/or psychopharmacological treatment (Ryan et al., 2012). Although the clinical validity of the DT has been shown by many studies, to our knowledge, none have assessed the DT neurobiological substrate. We tried to address

this issue by exploring the relationship between DT scores and brain metabolism in a sample of cancer patients, using a neuroimaging technique, the [18 F] PET-FDG.

Brain positron emission tomography (PET) is a nuclear medical imaging technique that produces a three-dimensional image of cerebral functional processes. A positron emitting radioisotope (18 F) is injected in the subject with a biological active molecule. Positrons emitted by radioisotope annihilated in the tissues produce pairs of gamma rays that are detected and recorded to reconstruct a three-dimensional map of the concentration of the injected molecule. When the biologically active molecule is fluoro-D-glucose (FDG), an analogue of glucose, its concentrations will indicate tissue metabolic activity by virtue of the regional glucose uptake. A simultaneous computerized tomography scan (CT) performed on the patient during the same session results in a PET/CT scan with better anatomical localization and better quality reconstruction of brain metabolism.

Since chronic distress results in high basal activity of the hypothalamic–pituitary–adrenal axis (Burke, Davis, Otte, & Mohr, 2005; Heim, Newport, Mletzko, Miller, & Nemeroff, 2010; Lupien et al., 2009; Tashiro et al., 2001), we expected to find a positive correlation between DT scores and specific brain area activity involved in the hypothalamic–pituitary–adrenal axis. Our major research question is: do patients with higher DT scores show higher brain metabolism in the hypothalamic–pituitary–adrenal axis brain area? The relationships between brain metabolism and DT subscales (Emotional and Physical Problems), anxiety and depression measures (HADS-Anxiety/-Depression) were also investigated.

Method

Participants

Cancer patients were enrolled from those who planned to undergo a whole-body [18 F]FDG PET on a clinically routine basis for cancer staging. Eligibility for the study required no neurological, neuropsychological or psychiatric disorders and no use of medications that could potentially alter brain metabolism or stress level. After approval by the ethical committee of San Giovanni Battista University Hospital, each patient gave his or her written informed consent to participate in the project. Twenty-one patients (14 men, age = 56 ± 12 years, all right-handed) participated in the study. Cancer diagnosis was lymphoma for the majority of the patients (n = 15; 71%; 12 non-Hodgkin and 3 Hodgkin subtype), whereas a minority had other diagnoses

(n = 6; 29%; one ovarian, one bladder, three lung and one rectal). None had previously received systemic chemotherapy treatment. Cancer staging, indicating the severity of the cancer and how widespread a cancer is, was reported in the Overall Stage Grouping (I–IV) in accordance with the American Joint Commission on Cancer/ International Union Against Cancer TNM Staging for solid cancers and the Ann Arbor Staging for lymphomas. The cancer grading was on a 4-item scale (G1–G4) with G1 and G4 indicating well-differentiated and poorly differentiated cells, respectively. A stage of 1 indicates a low severity, whereas a stage of 4 indicates a high severity of cancer. Table I shows the demographic and clinical patient characteristics.

All patients underwent neuropsychological and psychological assessment before the brain [18 F]FDG PET, on the same day. The neuropsychological battery was administered in order to exclude patients with cognitive deficits from the study. None were excluded.

Neuropsychological assessment

A neuropsychological test battery was used to assess neurocognitive functions, including attention, memory, language and frontal executive functions. Each patient was administered the following instruments: the mini–mental state examination assessing global cognitive status, Trail Making Test B assessing attention ability, phonemic fluency assessing mental flexibility and Short Story Test assessing memory and specifically the ability to learn new information.

Psychological assessment

The DT and two Problem Checklist DT subscales (Emotional Problems and Physical Problems) and the HADS were used to assess distress and anxiety and depression, respectively.

The DT (Holland, 1997; Roth et al., 1998) is a Numbers Rating Scale asking the patient to describe

his or her level of distress during the last week on a 0 (no distress) to 10 scale (extreme distress). In addition, patients were asked to indicate, in a ‘yes’ to ‘no’ format, if any of a list of 35 problems in different areas (practical problems, five items; relational, three items; emotional, six items; spiritual/religious, one item; physical, 21 items) was present in the last week. In the present study, only Emotional and Physical Problems were analysed. A cut-off score ≥4 on the DT was used to identify ‘cases’ according to the Italian normative data (Grassi et al., 2013; Grassi, Sabato, Rossi, Marmai, & Biancosino, 2009).

The HADS (Zigmond & Snaith, 1983) is a 14-item (each itemrated 0–3) self-report scale to measure anxiety (HADS-Anxiety, seven items, range score 0–21) and depression (HADS-Depression, seven items, range score 0–21). Scores of 0 and 21 indicate the minimum and maximum scores, respectively. A cut-off ≥8 indicates cases of clinical anxiety and depression. HADS was administered in the Italian version that was validated on a sample of cancer patients (Costantini et al., 1999; Grassi et al., 2009).

Positron emission tomography scanning

In a quiet waiting room, the participants, in a supine position, were asked to refrain from moving and instructed 'to keep their eyes closed, to not engage in any structured mental activity such as counting, rehearsing, etc., and to avoid falling asleep'. They were then blindfolded and ear-plugged before receiving intravenously about 4.5–5.5 MBq kg1 of 2-deoxy-2-[18 F] FDG. About 30 min later, a PET/CT scan was performed by a Philips Gemini scanner (Philips Medical System, Cleveland, Ohio, USA). The brain scan acquisition took 20 min. Reconstructed brain images had a dimension of 128 × 128 × 90 voxels (the threedimensional equivalent of a pixel, a small volume region of 2×2×2mm3). After the planned wholebody [18 F]FDG PET/CT examination was performed, the coronal, sagittal and transverse data sets were reconstructed using a three-dimensional iterative technique (row action maximum likelihood algorithm) and corrected with single scatter simulation.

Statistical analysis

The [18 F]FDG-PET brain images were pre-processed, and statistical analyses were performed using Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk/spm) running on MATLAB 7.5 software. SPM is a statistical approach that uses a univariate general linear model. For every brain voxel (a small three-dimensional region), we computed the correlation between the local metabolism and variables of interest, accounting for potential confounding variables (e.g. age and sex). The results were visualized in a SPM image reporting the voxel-wise statistical results (e.g. p-values for every voxel).

The pre-processing consisted of spatial normalization to align the participants' brains, of count normalization and of image smoothing in order to magnify the signal-to-noise ratio of the data. All images were nonlinearly spatially normalized into the Montreal Neurological Institute space and smoothed with an isotropic Gaussian kernel of 12mm full-width half maximum. Confounding effects of global activities differences were

removed by normalizing the count of each voxel to the mean count of a standard region of interest (ROI) located in the brainstem pons in order to avoid biased normalization (Borghammer, Cumming, Aanerud, & Gjedde, 2009). This region was chosen as it maintains good metabolic stability with ageing. Only voxel values greater than 80% of the whole-brain mean glucose metabolism were included in the analysis to exclude the majority of voxels that were outside the brain gray matter.

To link the psychological measures with metabolic patterns, we computed SPM with test scores (DT or Emotional Problems or Physical Problems or HADS) as independent variables, age and gender as confounds and regional brain glucose metabolism as the dependent variable.

To minimize false positives, all SPM results were thresholded at $p<0.005$ uncorrected for multiple comparisons, with an extent threshold cluster of 20 voxels.

We classified the SPMresults inside the cortex using the Anatomical Automatic Labelling atlas (Tzourio-Mazoyer

Table I. Clinical and demographic characteristics

Data		
Patients [M/F]	21 [14/7]	
Age [y]	56 ± 12	
Education [y]	11 ± 4	
Solid cancer [M/F]	6 [3/3]	
Staging [I–II–III–IV]	4–0–2–0	
Lymphoma [M/F]	15 [11/4]	
Staging [I–II–III–IV]	0–2–6–7	
Grading [G1–G2–G3–G4]	10–4–7–0	
Age at onset [y]	56 ± 14	
Disease duration [months]	2 ± 2	
Neuropsychological	Cut-off	Deficit (%)
MMSE	27.8 ± 1.4	23.8 0
TMT-B	69 ± 33	283 0
Phonemic fluency	36.0 ± 8.8	17.5 0
Short Story	9.9 ± 3.1	4.5 0
Psychological	Cut-off	Cases (%)
HADS-Anxiety	7 ± 3	8 48
HADS-Depression	5 ± 3	8 19
Distress Thermometer	4 ± 2	4 48
Problem Checklist-Emotional	2 ± 2	— —
Problem Checklist-Physical	3 ± 3	— —

M/F: male/female; y: years; MMSE: mini–mental state examination; TMT-B: Trail Making Test B; HADS: Hospital Anxiety and Depression Scale.

The cut-off indicates the score less than or greater than that the patient shows a deficit (a problem in a specific domain) or can be considered ‘a case’.

et al., 2002). For the results in the brainstem, we referred to a specific atlas (Naidich et al., 2009).

We also performed an analysis on a previously selected ROI: the hypothalamus. This brain region is well known to be implicated in stress processing and is a key area in the regulation of hypothalamic–pituitary–adrenal axis.We extracted the mean metabolic raw value of the ROI using the SPM toolbox MarsBaR (Brett, Anton, Valabregue, & Poline, 2002) to better elucidate the role of demographic and clinical characteristics in hypothalamic activity.

Firstly, we used non-parametric Mann–Whitney U, Kruskal–Wallis H or Spearman correlation tests to investigate possible metabolic ROI differences for sex, age, DT, depression, type of cancer (solid or lymphoma), disease duration, staging and grading. Then, we used a linear regression to predict ROI metabolism with a stepwise method, using all the aforementioned variables together, to understand which set of clinical and demographic variables best captured the ROI metabolic variations among participants.

Finally, we binarized the DT score using the clinical screening cut-off of 4 to obtain two groups: one distressed and one not distressed. We used binary logistic regression using sex, age, depression, type of cancer, disease duration, staging, grading and ROI metabolism to find what set of variables was best in classifying the participants at risk of distress.

Results

Neuropsychological and psychological data

The neuropsychological and psychological results are reported in Table I. All the patients scored greater than the cut-off in all the neuropsychological tests, meaning that they were all eligible for the study. According to neuropsychological test scores, none of the patients showed deficits in attention, memory, language and frontal executive functions. According to the cut-off scores, distress (DT) was found in 48% (10/21) of patients, depression (HADS-Depression) in 19% (4/21) and anxiety (HADS-Anxiety) in 48% (10/21).

Correlation between Distress Thermometer and positron emission tomography

The DT scores showed a significant positive correlation with regional brain glucose metabolism in the hypothalamic and midbrain areas immediately below the thalamus, especially the periventricular areas (Figure 1a).

The cluster was compatible with the dorsalmedial

hypothalamus, the periventricular nucleus of the hypothalamus, the periventricular–periaqueductal gray region of the midbrain, the raphe dorsal nucleus and the inferior and superior colliculi of the midbrain, but the smoothing and the resolution of the PET scans did not allow certain identification.

Correlation between Distress Thermometer Problem List and positron emission tomography

The presence of Physical Problems (Figure 1b) showed a significant positive correlation with activity in the same areas of the DT, but the clusters extended to additional areas including caudate, thalamus, globus pallidus, putamen, bilateral amygdala (Figure 1b), hippocampus, parahippocampus, high pons and medulla.

The high pons cluster was compatible with the locus coeruleus and the medulla with the ventrolateral and ventromedial medulla complexes, but the smoothing and the resolution of the PET scans did not allow certain identification.

The presence of Emotional Problems showed a significant positive correlation with the activity of four clusters: in the hypothalamus, in the midbrain in front of the right amygdala, in the high pons and in the medulla (Figure 1b). These areas largely overlap the regions in which activity showed correlations with the Physical Problems scores.

Correlation between Hospital Anxiety and Depression Scale (HADS)-Anxiety/HADSDepression and positron emission tomography

The HADS-Anxiety scores did not correlate with regional brain glucose metabolism in any areas.

The HADS-Depression scores (Figure 1c) showed the most extended pattern of positive correlations, including, apart from subcortical areas linked to the hypothalamic–pituitary–adrenal axis, activity of many cortical areas: frontal cortex, temporal cortex, cingulated gyrus, the bilateral insula and cerebellum. No area showed negative significant correlations with the presence of depression.

Analyses on hypothalamus region of interest

We did not found any significant correlations for age, depression and disease duration or differences for sex, staging and grading. Only DT scores were highly correlated with ROI metabolism ($p<0.01$). The stepwise regression selected a model with only the DT as dependent variable ($p<0.01$) and an adjusted R2 of 0.56:
ROI = 10.5 + 0.31 × DT. The logistic stepwise regression selected a model with ROI metabolism as the best

predictor of distressed status and a classifying efficiency of 90%.

Discussion

From a neurobiological point of view, prolonged and/or chronic exposure to physical or psychological stressors, as occurs in cancer patients, may have consequences for the brainstem and forebrain limbic structures that produce downstream effects (Joëls & Baram, 2009) through the sympatho–adrenomedullary and hypothalamic–

pituitary–adrenocortical axes, which by reacting to stress, help maintain homeostasis (Ulrich-Lai & Herman, 2009).

The principal finding of the present study was the positive correlation between DT scores and the activity of the brain areas involved in stress responses in a population of cancer patients without cognitive deficits.

We showed that the higher the DT score, the higher the brain metabolism in brain areas regarding different aspects of the elaboration, modulation and responses to stress. Specifically, the hypothalamus integrates limbic and brainstem inputs, with respect to homeostatic feedback, whereas the midbrain and medulla are involved in autonomic, behavioural and hormonal regulation (Ulrich-Lai & Herman, 2009). The periventricular nucleus and periventricular–periaqueductal gray region are involved in the cognitive, emotional and neuroendocrine processing of stressful events (Joëls & Baram, 2009). The superior colliculus is involved in multisensory integration (Stein & Rowland, 2011), which is important to connect different bodily sensations during stress arousal. In addition, the extracellular serotonin levels in the inferior colliculus can change rapidly in response to stressful situations (Hall, Sell, Chester, & Hurley, 2012). Also, the brain stem plays major roles in the sympathetic and parasympathetic activities that are crucial to stress. The lack of correlation between the DT and higher cortical areas activity possibly implicates that DT is not related to appraisal or to resource utilization (higher cortical processes) but to 'lower' and basic processes of the stress response (Taylor et al., 2008).

Emotional Problems and Physical Problems were correlated with brain metabolism and shared the same common pattern of correlation of the DT and included additional areas. Specifically, Emotional Problems scores showed a significant correlation with the hypothalamus and medulla activity, whereas Physical Problems showed a significant correlation with activity in the brainstem (locus coeruleus and the medulla), limbic forebrain structures (amygdala, hippocampus) and basal ganglia

(caudate, globus pallidus, putamen). All these brain areas
Figure 1 Metabolic correlates of Distress Thermometer, Problem Checklist and Hospital Anxiety and Depression Scale (HADS)-Depression.
(a) Distress Thermometer as the independent variable and metabolism as the dependent variable. In light grey with black border areas
whose activity correlates positively with DT scores. (b) Problem Checklist as independent variable and metabolism as dependent variable.
In light grey with black border areas whose activity correlates positively with Physical Problems scores, in grey areas whose activity correlates
positively with Emotional Problems scores, in black amygdala. (c) HADS-Depression as the independent variable and metabolism as the
dependent variable. In grey with black border areas whose activity correlates positively with HADS-D scores. Age and gender were used
as control variables in all Statistical Parametric Mapping; all results were thresholded at $p<0.005$ uncorrected for multiple comparisons,
with an extent threshold cluster extent (Ke) of 20 voxels. Figure is in neurological convention—the left areas are represented on the left,
the right areas on the right. Abbreviations are as follows: AMG, amygdala; HYP, hypothalamus; L, left; LC, locus coeruleus; MID, midbrain;
R, right; VLM, ventrolateral medulla

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play an important role in stress modulation, and in particular, the amygdala and the hippocampus regulate the hypothalamic–pituitary–adrenal axis activity (Ulrich-Lai & Herman, 2009). In addition, the amygdala plays an important role in fear and its maintenance and is essential in mediating enhanced emotional memory consolidation that occurs under stress (Roozendaal, McEwen, & Chattarji, 2009). But, the efficient encoding of emotionalmemories can become a disadvantage when severe stress turns into chronic distress (Roozendaal et al., 2009).

Hospital Anxiety and Depression Scale-Depression scores not only showed significant correlations with activity in many cortical and subcortical areas, including the same areas that correlated with the DT, Emotional Problems and Physical Problems scores but, as reported in previous studies, also with the activity of structures involved in emotional processing, such as the cingulate gyrus (Feder, Nestler, & Charney, 2009), the cerebellum (Baldaçara et al., 2011) and the frontal cortex (Arnsten, 2009). The simultaneous increased activation in limbic and frontal structures could refer to the high cognitive mechanisms involved in depression, such as rumination or exaggerated self-reflection (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010).

This result supports the difference between the neurobiological correlates of distress and depression as two distinct psychological entities. Indeed, the shared

common areas of correlation between the DT and HADS-Depression scores and brain activity account for how depression and distress are interrelated.

The correlation between DT scores and hypothalamic metabolism at rest was corroborated by both non-parametric analyses and multiple regression. These analyses illustrated that DT scores were the best predictor, among all the other clinical and demographical variables, of the hypothalamic metabolism, a key area of the hypothalamic–pituitary–adrenal axis. In addition, logistic regression showed that the hypothalamic metabolism was the best indicator to classify patients as distressed according to the DT cut-off.

The importance of the hypothalamus was underlined by a previous study that investigated the brain correlates of being diagnosed with lung cancer (Golan et al., 2009). Specifically, in this study, cancer patients showed a statistically significantly higher right cerebellar metabolism compared with the control group. The authors suggested that this finding may be related to the role of the cerebellumin immune regulation because of its proximity to the nucleus tractus solitarius and its connections with the hypothalamus. Also, Tashiro and colleagues pointed out that brain activity alterations related to psychological distress in emotional processing areas, with connections to the hypothalamus, in cancer patients (Tashiro et al., 1999). Since excessive stress is a risk factor for the development and exacerbation of psychological and psychiatric disturbances, including depression, this last evidence seems to provide neurobiological support to clinical studies underlining the importance of early identification of psychological distress in oncological settings.

Limitations of the study

This is the first study to have investigated the relationship of DT scores and neurobiological substrate; so, directly comparable data are unavailable. Further studies are needed in order to confirm our results. Because of the small number of subjects, replication of the study in larger samples is necessary.

In conclusion, the DT scores in our sample of cancer patients showed significant positive correlations with the activity of the main brain areas involved in the stress response, and although preliminary, these results provide evidence supporting the neurobiological validity of the DT. These results provided relevant neurobiological evidence about the effectiveness of the DT in detecting distressed patients, suggesting that patients with high DT scores are effectively more distressed, since they showed an increased activity in brain areas

involved in the stress response.

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