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The behavioural approach system and placebo analgesia during cold stimulation in women: A low-resolution brain electromagnetic tomography (LORETA) analysis of startle ERPs

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ABSTRACT

Personality traits have been shown to interact with environmental cues to modulate biological responses including placebo effects. We assessed the behavioural approach system (T-BAS) and its facets (goal drive persistence, GDP; reward interest and reactivity, RI and RR; Impulsivity, Imp) using the Reinforcement Sensitivity Theory Personality Questionnaire (RST-PQ; Corr & Cooper, 2016). Participants received three treatments: Baseline, Pain, and Placebo (pain plus a sham cream). Pain was produced by administering the cold-cup-test (CCT). We used exact low-resolution brain electromagnetic tomography (eLORETA) analysis of event-related potentials elicited by auditory-startle probes to identify regional sources of activity changes as predictors of T-BAS and its facets. We calculated pain minus placebo differences for pain and distress ratings and regional current density. We failed to find significant associations of RST-PQ traits with placebo-induced pain and distress reductions. However, multiple regression analyses and covariance analyses showed that, during placebo analgesia as compared to pain treatment, a lower activity in the primary somatosensory cortex (S1) was associated with higher T-BAS, and RI, whereas lower activity in the ACC was associated with higher T-BAS, RR, and Imp. Findings suggest that placebo analgesia may represent a form of reward responding and likely offer paths of identifying BAS traits that are liable to modulate placebo analgesic responses.

1. Introduction

Placebo analgesia (PA) is a widely studied phenomenon where the administration of either a pharmacologically inert substance in the guise of analgesic drug or a sham procedure has a pain-relieving effect. The medical uses of placebos for analgesic purposes illustrate well-documented powerful forms of social influence on pain (Finniss, Kaptchuk, Miller, & Benedetti, 2010) and are very important for the design and evaluation of clinical trials (Price, Finniss, & Benedetti, 2008).

Neuroimaging studies indicate that the anterior and posterior insula, amygdala, anterior cingulate cortex (ACC), dorsal and ventral striatum, and the orbitofrontal cortex (OFC) are all involved in pain as well as reward processing (e.g., Fujiwara, Tobler, Taira, Iijima, & Tsutsui, 2009; Leknes, Lee, Berna, Andersson, & Tracey, 2011) and suggest that avoidance of aversive outcomes activates OFC comparable to receiving rewarding stimuli (Kim, Shimojo, & O'Doherty, 2006). Research has shown that personality traits and environmental cues modulate biological responses associated to placebo effect. Across the years, several parallel multifaceted dispositional measures of individual tendency to experience positive emotions and well-being have been proposed as appropriate and useful predictors of placebo responding (Geers, Kosbab, Helfer, Weiland, & Wellman, 2007; Nes & Segerstrom, 2006; Scheier & Carver, 1987). Trait optimism and trait anxiety were found to be positive and negative reproducible predictors of PA (Geers, Wellman, Fowler, Helfer, & France, 2010; Morton, Watson, El-Deredy, & Jones, 2009). Functional neuroimaging (fMRI) studies also suggest an association between optimism or self-esteem and the activation of anterior regions of the cortex (e.g., Sharot, Riccardi, Raio, & Phelps, 2007). Schweinhardt, Seminowicz, Jaeger, Duncan, and Bushnell (2009) found that a combination of novelty seeking, behavioural drive, and fun seeking accounted for 30% of the variance in the placebo analgesic response. They also obtained that the magnitude of PA was associated with greater grey matter density in several brain regions, including the ventral striatum, insula, and prefrontal cortex. Similar findings were reported in a molecular imaging study (e.g., Peciña et al., 2013) showing that a composite of positively valenced traits (Ego-Resiliency, NEO-Altruism, NEO-straightforwardness) were positive predictors of placebo analgesic responses. Karjalainen et al. (2016), using positron emission tomography (PET) scan, found that BAS, but not BIS sensitivity (Carver & White, 1994), was positively associated with μ-opioid receptor (MOR) availability in frontal cortex, amygdala, ventral striatum, brainstem, cingulate cortex and insula. Strongest associations were

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observed for the BAS facet of Fun Seeking, indicating that endogenous opioid system underlies BAS, and that differences in MOR availability could explain inter-individual differences in reward seeking behaviour. Although these studies indicate that placebo responses may represent a form of reward responding based on positive expectations (Scott et al., 2007), the underlying brain mechanisms of the immediate effects of pain relief and their modulation by motivational personality traits have been poorly investigated.

A widely known theory of motivational personality traits is the Revised Reinforcement Sensitivity Theory (RST) of personality. The most recent version of the RST (Corr & McNaughton, 2012; McNaughton & Corr, 2004, 2008) postulates three major neuropsychological systems controlling approach and avoidance behaviour: (1) the fight-flight-freeze system (FFFS) that is activated by aversive stimuli; (2) the behavioural approach system (BAS), activated by appetitive and positive emotion stimuli; and (3) the behavioural inhibition system (BIS), activated by goal conflict. This is a revision of the original RST formulated by Gray (1982) that conceptualized only two of these systems, the BIS and the BAS. Although most of the newer classes of RST questionnaires measure the BAS, as a unitary dimension (for a structural survey analysis, see Corr, 2016), there is compelling evidence that the BAS is multidimensional (Carver & White, 1994; Corr, 2008; Dawe, Gullo, & Loxton, 2004; De Pascalis, Fracasso, & Corr, 2016). Consistent with theoretical and empirical considerations of the rRST, a new questionnaire has been proposed, the Reinforcement Sensitivity Theory of Personality Questionnaire (RST-PQ; Corr & Cooper, 2016), developed on the basis of qualitative responses to defensive and approach scenarios. The RST-PQ disclosed a robust 6-factor structure: 2 unitary defensive factors, the FFFS, related to fear, and the BIS, related to anxiety; and four BAS facets (Reward Interest, RI; Goal-Drive Persistence, GDP, Reward Reactivity, RR; Impulsivity, Imp). The RST-PQ allows the separation of GDP, RI, and RR from Imp sub-factors of the BAS, making possible to test the unique predictive power of each sub-factor.

In the present work, we reprocessed part of an our waking-placebo ERP data published elsewhere wherein auditory startle stimuli were used as probes of pain processing (De Pascalis & Scacchia, 2016). We are pleased and honored to present our recent psychophysiology of personality findings in this special PAID issue for Robert Stelmack as a tribute to his teaching and orienting our research work.

Aim of this work was to highlight RST-PQ BAS facets[1] that are associated with placebo pain relief. We also examined the association of these traits with objective measures of placebo effects, i.e., placebo-induced auditory-startle changes in regional cortical current densities associated to pain relief. We used exact low resolution brain electromagnetic tomography (eLORETA) analysis (Pascual-Marqui, Michel, & Lehmann, 1994) on ERPs elicited by auditory startle stimuli delivered during pain and placebo-analgesia experience. This served to obtain the temporal activation profiles of cortical region of interests (ROIs), common to both pain and startle networks (Garcia-Larrea & Peyron, 2013; Kumari et al., 2005; Neuner et al., 2010). We expected that BAS facets, being dopamine-related personality traits, would partially predict the magnitude of self-reported placebo analgesic experience and would be related with objective measures of placebo effects as placebo-induced reductions of activity within dorsolateral prefrontal cortex, S1 and ACC, known as cortical regions sensitive to placebo pain relief (Karjalainen et al., 2016; Peciña et al., 2013; Schweinhardt et al., 2009; Sharot et al., 2007). Further aim of this study was to test, in terms of placebo-induced cortical activity changes, if the four BAS facets exhibit a unique predictive power, or they are redundant, mainly for the distinction of RI and RR versus Imp.

[1] The association of BIS and FFFS with placebo-pain relief and sources of cortical activity is reported in a study of our own published in the current issue of this journal. In this study we highlighted the major cortical regions sensitive to pain and distress reduction by placebo treatment.

2. Methods

2.1. Participants

We had 55 participants (M = 23.4, SD = 2.2 years) for electroencephalographic (EEG) data analysis including pain rating scores, but only 52 were available for data analyses including personality scores. More details can be found in our paper reported in this issue of PAID journal (De Pascalis & Scacchia, 2017).

2.2. Questionnaires

Participants completed the State Anxiety Inventory (STAI-Y1; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1988) and RST-PQ (Corr & Cooper, 2016) that measures three major systems: FFFS, BIS, total BAS (T-BAS) and its four facets: GDP, RI, RR, and Imp. Cronbach's α values T-BAS, GDP, RI, RR, and Imp respectively were 0.86, 0.85, 0.75, 0.78, and 0.76).

2.3. Sham analgesic cream

Sham analgesic cream was a simple pale yellow perfumed cream, labeled as *Anedicaine Cream*, a drug known to be a strong local analgesic free from side effects. A more detailed description of verbal suggestion, sham analgesic cream compound, pain induction, treatments, auditory startle, and EEG processing is given elsewhere (for details see De Pascalis & Scacchia, 2016).

2.4. Pain induction, manipulation, and treatments

Pain was produced by administration of the cold cup test (CCT) requiring participant to hold in the right hand a cup at −10 °C for 3.7 min. PA was initially produced by manipulation, in which the intensity of pain was surreptitiously reduced after the administration of a sham analgesic cream. Manipulation testing was followed by three treatments: (1) Baseline (auditory-startle alone), requiring to hold for 3.4 min in the right hand a cup at 35 °C; (2) Pain (auditory-startle alone plus CCT) as in (1), but the holding time and temperature of cold cup were respectively of 3.7 min and −10 °C (Chen, Chang, & Arendt-Nielsen, 2000); (3) Pain as in (2), but including suggestive administration of *Anedicaine Cream* for pain relief (PA treatment, i.e.,auditory-startle alone plus CCT plus sham cream).

During manipulation condition and following Pain and Placebo treatments, participants rated their pain and distress sensations on a 0 to 100 'Numeric Rating Scale' (Jensen, Karoly, & Braver, 1986). Numerical pain difference scores (NPDSs) and numerical distress difference scores (NPDSs) were calculated by subtracting numerical pain scores (NPSs) and numerical distress scores (NDSs), obtained during Placebo, from numerical scores obtained during pain treatment. Positive values of this measure indicate pain/distress reduction, whereas negative values denote pain/distress increase.

2.5. Acoustic startle stimuli

The acoustic startle stimulation was binaurally presented through headphones and consisted of three trial blocks. Before starting the first block, a 2 min adaptation period was given with 70 dB background broadband noise (0–44 kHz). This period included 5 acoustic stimuli at 115 dB (7–10 inter-stimulus-interval, ISI). Each block included 24 acoustic stimuli delivered above the background white noise. Of the 24 acoustic stimuli, 10 were pulse (P) stimuli and 14 were pairs of acoustic stimuli, a prepulse followed by a pulse with a lead interval of 120 ms. P startle stimuli were acoustic white-noise probes (115 dB, 40 ms, instantaneous rise time < 1 ms). In order to avoid habituation, i.e., reduced responding across stimulus type, P and prepulse-pulse (PP) stimuli were presented in pseudorandom order to ensure