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Testing an anxiety process biomarker: Generalisation from an auditory to a visual stimulus

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ABSTRACT

We have previously reported an anxiolytic-sensitive human EEG biomarker, goal conflict specific rhythmicity (GCSR), using an auditory stop signal task (SST). Here we test if a visual SST could allow testing of GCSR in people with hearing impairments. The visual SST produced GCSR within the 4–12 Hz band at the expected right frontal site, F8, but to a lesser extent than in previous auditory SSTs, possibly due to response instability. Positive GCSR appeared to be reduced by both buspirone (10 mg), and triazolam (0.25 mg), as previously; negative GCSR was increased. However, neuroticism, trait anxiety and Behavioural Inhibition System scores failed to show consistent positive correlations with GCSR, contrary to prediction. The visual SST generates anxiolytic-sensitive GCSR; but its limited extent and unexpected personality correlations suggest it needs further development to obtain quantitative equivalence with the auditory SST.

1. Introduction

Anxiety disorders have a major mental health impact (Kessler and Greenberg, 2009), with growing numbers of people seeking primary and secondary medical care, increasing the burden on governments and societies (Somers, Goldner, Waraich, & Hsu, 2006). In the United States, income lost due to psychiatric disorders totals more than $200 billion per year (Eaton et al., 2008), where anxiety disorders are contributing highly as more people are suffering from these disorders in comparison to other types of mental illness. Anxiety disorders are, at present, usually diagnosed by the American Psychiatric Association's Diagnostic and Statistical Manual, currently in its 5th Edition (DSM-5) (APA, 2013) or by the International Classification of Diseases, currently in its 10th edition (ICD-10) (WHO, 2010). DSM-5 and ICD-10 diagnose anxiety disorders based on a patient's reports of experiencing aversion together with characteristic behavioural and physiological responses (e.g. avoidance, vigilance and arousal). But these things can be present normally; and so DSM-5 and ICD-10 require them to be excessive, persistent, distressing, and functionally impairing to meet clinical criteria for an anxiety disorder. Neither anxiety disorders nor the distinction between anxiety and fear/phobia are biologically defined. Several phobias are included within "anxiety disorders" by DSM-5 whereas ICD-10 separates phobia from anxiety. Conversely, ICD-10 groups anxiety and phobia together with additional disorders within a broader class of "neurotic, stress-related and somatoform disorders". The critical problem with both ICD-10 and DSM-5 is that they distinguish only superficial patterns of symptoms (e.g. worry; panic attacks) or the situations associated with them (e.g. social scrutiny, specific objects) and have no objective biomarker to define any specific underlying cause of disorder.

We (McNaughton, Swart, Neo, Bates, & Glue, 2013) previously reported a possible human anxiety-disorder-specific biomarker using an auditory Stop Signal Task (SST). However, this version of the SST had unequal number of trials in the groups used for analysis, which is statistically undesirable, with the groups continuous with each other. It also produced Goal Conflict Specific Rhythmicity (GCSR) only at 9–10 Hz – a narrower band than the rodent rhythmicity model (McNaughton, Kocsis, & Hajos, 2007) that is a key part of the Behavioural Inhibition System (BIS) theory (Gray and McNaughton, 2000) on which the GCSR test was based. We have recently modified the SST to produce balanced trials in clearly separated groups (Shadli, Glue, McIntosh & McNaughton (2015)). This modified SST produced the expected broad band (4–12 Hz) GCSR, which was sensitive to three distinct chemical classes of anxiolytic

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drug (triazolam, a benzodiazepine agonist; buspirone, a $5HT_{1A}$ agonist; and pregabalin, a calcium channel inhibitor) and tended to correlate moderately but positively with neuroticism and trait anxiety.

Our improved version of the SST used an auditory stop signal as in our previous experiments but was partially based on the methods of Carter et al. (2003), who used a visual stop signal. So, here, we substituted a visual stop signal for our previous auditory one and challenged the SST with anxiolytic drugs and personality questionnaires to see if a visual SST could generate an equivalent GCSR to the auditory SST and so provide a version of the test suitable for hearing impaired patients.

2. Method and materials

2.1. Participants

There were 30 participants (20 female, 10 male; age 18–25 years; with 4 excluded because of a computer failure) for the first (drug) experiment. There were three different treatment groups in the drug experiment: placebo (4 male, 6 female); buspirone (10 mg; 2 male, 6 female); and triazolam (0.25 mg; 3 male, 6 female). The groups were balanced on entry (1:1:1) with a computer generated block size of three. Buspirone and triazolam doses and administration were the same as used previously (McNaughton et al., 2013). Note that these doses are at the bottom end of the clinical range and would not be expected to produce sedation. Treatments were over encapsulated to make them homogenous visually and were administered double blind. After exclusions based on EEG artefact and computer failure, the groups remained approximately balanced. For the second experiment, we included the personality data from the placebo group of the drug experiment and tested a further 10 participants (2 participants' data excluded due to artefacts, leaving 4 female and 4 male), age ranging from 18 to 25 years for a total of 10 female and 8 male overall. Participants were recruited from Student Job Search, were right handed, reported no psychological disorders and they were not taking any drug related to mental disorders. They provided written consent prior to the experiments; with consenting for the drug experiment undertaken by a psychiatrist (PG). They each received NZ$30 as a reimbursement in recognition of the inconvenience and costs related to taking part in the study. The experiments were approved by the University of Otago Human Ethics Committee (**approval numbers: DP 10/07 & 13/035**).

2.2. Procedure

The procedure was as in Shadli et al. (2015) except for the substitution of a visual stop signal for the auditory one. Participants filled out the EPQ-R (Eysenck and Eysenck, 1975), BIS/BAS scale (Carver and White, 1994) and STAI-Trait questionnaires (Spielberger and Gorsuch, 1983) after arrival at the laboratory. GCSR in the placebo group (N = 10 only) appeared, unexpectedly (Neo and McNaughton, 2011; Shadli et al., 2015), to be negatively correlated with neuroticism, trait anxiety, and Behavioural Inhibition System scores. So, we undertook experiment 2, where we combined these placebo data with an additional 10 participants' data and without inclusion of any drug groups. For the drug experiment, participants were first administered white coated capsules before filling out the questionnaires and started the SST 60 min after taking their capsules, when peak blood levels would be anticipated. The participants were then prepared for EEG recording. We used two different EEG systems. For the drug experiment, we used a Waveguard (Ag/Agcl) cap with a 32-channel ASA Neurotechnology system. For additional participants in experiment 2, we used an Electro-cap (Electrocap International) with an 8-channel BioRadio (Great Lakes Technology) recording system. The sampling rate for analysis was 128 Hz, band pass was 1–36 Hz, and impedance was reduced to below 5 kΩ. Once acceptable impedances were obtained, deliberate eye-blink traces and relaxation-induced alpha rhythm were assessed to screen for oddities in the recordings and further electrode adjustments made where necessary. The STAI-State questionnaire was then administered, followed by the SST task. Immediately after the SST task, they were given the STAI-State questionnaire again.

2.3. Stop signal task

The SST used in these experiments was derived from that originally used by Aron and Poldrack (2006) and in our previous experiments testing personality and anxiolytic drugs (McNaughton et al., 2013; Neo and McNaughton, 2011). As in Shadli et al. (2015), it had the following modifications from the original version: (1) short and long, but not medium, delays were controlled by go response time using the method of Carter et al. (2003); (2) colour was added to the fixation circle to increase the discriminability of the go and stop stimuli; (3) feedback on correct/incorrect performance was added after each trial; 4) "slow" feedback was provided when the participant's Go reaction time during stop testing exceeded 1.5 times their reaction time in pretesting with pure Go trials. The only change from Shadli et al. (2015) was that an exclamation symbol (!) presented in the fixation circle, rather than a tone, was used as the stop signal. For fuller details, stimulus images, and a schematic of the procedure, see supplementary materials.

On Go trials, a fixation circle (white) was presented on the centre of the screen against a black background. A left/right white arrow appeared in the circle (changed to green) 500 ms later. Participants were instructed to press the left/right mouse button as quickly and accurately as possible in response to the left/right arrow, respectively. On Stop trials, the stop signal (! symbol in red circle) was presented at variable delays and participants were told to withhold their mouse click on these trials. The SST consisted of three blocks each of 128 trials, with a stop signal being presented once in each 4 trials, so each block contained 32 Stop trials and 96 Go trials. It was preceded by a practice block of 16 Go trials (designed to develop a pre-potent Go response tendency and to estimate the Go RT on which to base the initial stop trial delay values).

Within each 128-trial block of the SST, the stop signal delays were systematically varied between trials. This was controlled using a staircase-like tracking system. This modified SST had 3 nominal "staircases" delivering short, medium, and long SSDs. The short and long SSD values were set to 20% and 80%, respectively, of the average GO reaction time over the previous 16 GO trials. The medium staircase was set to start at 45% of pre-training GO reaction time but then tracked responding (increasing after successful stopping and decreasing after failed stopping) as with the staircases used by Aron and Poldrack (2006) but in 30 ms rather than 50 ms steps and with a restriction that the SSD could never get closer than 50 ms to the current value of either of the other staircases. The medium staircase was expected, therefore, to track the 50% correct stopping point where maximum conflict is expected in the BIS theory (Gray and McNaughton, 2000).

2.4. Data analysis

The data analysis procedure was as in our previous experiments (McNaughton et al., 2013; Neo and McNaughton, 2011). Residual mains noise was filtered using a simple 3 point running mean with an effective cut off of 43 Hz. Eye blink artefacts were removed, leaving residual EEG, by automatically fitting a template of the ballistic components of each eye blink to activity at Fp1 and then subtracting this from other channels after scaling with a least squares technique (Gratton, 1998; Neo, Thurlow, & McNaughton, 2011). Then,