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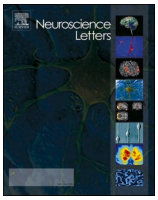

Functional connectivity across dorsal and ventral attention networks in response to task difficulty and experimental pain

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ABSTRACT

The dorsal and ventral attention networks (DAN & VAN) provide a framework for studying attentional modulation of pain. It has been argued that cognitive demand distracts attention from painful stimuli via top-down reinforcement of task goals (DAN), whereas pain exerts an interruptive effect on cognitive performance via bottom-up pathways (VAN). The current study explores this explanatory framework by manipulating pain and task demand in combination with functional near-infrared spectroscopy (fNIRS) and Granger Causal Connectivity Analyses (GCCA). Twenty-one participants played a racing game at low and high difficulty levels with or without experimental pain (administered via a cold pressor test). Six channels of fNIRS were collected from bilateral frontal eye fields and intraparietal sulci (DAN), with right-lateralised channels at the inferior frontal gyrus and temporoparietal junction (VAN). Our first analysis revealed increased G-causality from bottom-up pathways (VAN) during the cold pressor test. However, an equivalent experience of experimental pain during gameplay increased G-causality in top-down (DAN) pathways, with the left intraparietal sulcus serving a hub of connectivity. High game difficulty increased G-causality via top-down pathways and implicated the right inferior frontal gyrus as an interhemispheric hub. Our results are discussed with reference to existing models of both networks and attentional modulation of pain.

1. Introduction

Selectivity is a fundamental characteristic of attention since the concept was first introduced to psychological research over a century ago [25]. A requirement for humans to select part of the information available in their sensory field is necessitated by the limited capacity of the cognitive system [5,27,42] and the requirement to prioritise specific stimuli for action preparation [1]. The natural consequence of this selectivity is competition between stimuli that are presented simultaneously for subsequent perceptual and cognitive processing [53].

The introduction of painful stimulation during cognitive performance provides an archetypal example of competition between concurrent stimuli due to selective attention. The experience of pain is salient for the person, which creates an attentional bias towards stimuli associated with pain [10,14]. This bias can reduce attention to a cognitive task and degrade performance [34,39,38]. Similarly, performance of cognitive tasks that are demanding, engaging and highly motivating create a bias in the opposite direction, distracting attention from painful sensation and increasing pain tolerance [6,33,51,55,54]. A number of theoretical perspectives have been proposed to account for the interactive effects of pain and cognitive demand on selective attention, from biological [52] to cognitive [31], motivational [63], and affective mechanisms [48] – see Torta et al. [62] for review.

In order to understand how this selective mechanism works in the presence of competing stimuli, it is important to decompose attention into distinct functions [29]. Posner & Petersen [47] described three types of attention: (1) executive attention to sustain focus on task-relevant stimuli by filtering task-irrelevant stimuli, (2) alerting attention to modulate readiness to respond to an anticipated stimuli, and (3) orienting attention to select specific types of stimuli from the sensory field – see also Petersen & Posner [44]. All three functions are associated with distinct neuroanatomical structures [17,50] and can function independently, but attentional control is achieved by a dynamic process of coordination that allows the person to sustain, switch, reorientate and adjust the focus of attention [70].

There are specific categories of stimuli, such as painful sensations,

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which can trigger the involuntary capture of attention. This pattern of exogenous attention is automatic, stimulus-driven, and bottom-up, in contrast to the conscious, goal-driven, top-down qualities of endogenous attentional control [15]. An endogenous/exogenous distinction is the basis for a neuroanatomical model that describes how attention is directed, reorientated and redirected [2,7–9,20,28,37,59,61,65]. This model includes a dorsal attention network (DAN) that is activated in a top-down fashion to reinforce endogenous focus on goal-relevant stimuli. The DAN is bilaterally located with core regions at dorsal frontal cortex (Frontal Eyes Field: FEF) and the dorsal parietal cortex, particularly the superior parietal lobule and the IntraParietal Sulcus (IPS) [8,9]. The DAN is organised bilaterally with each hemisphere dedicated to endogenous attention in the contralateral area [37]. Causal analyses (e.g., Granger, Dynamic Causal Modelling) has revealed that DAN exerts a top-down influence on occipital areas during spatial orientation to visual targets [4,66]. The DAN is complimented by the ventral attention network (VAN), which is responsible for reorienting attention to exogenous stimuli [8]. The VAN is located at two areas in the right hemisphere, the fronto-insular cortex, e.g., inferior frontal gyrus (IFG) and medial frontal gyrus (MFG), and the temporoparietal junction (TPJ) [2,8,20,28]. The VAN works in a bottom-up fashion; for example, when participants were presented with invalid cues for spatial visual attention, causal modelling indicated pathways from the visual areas at the occipital cortex to the right TPJ, which connected to the right IFG and IPS [66].

According to Corbetta et al. [8], the DAN and VAN work in a coordinated fashion, enabling a person to focus on task-relevant goals (DAN) while retaining a capacity to reorientate to salient and/or unanticipated stimuli (VAN). The resulting regulation of attention is characterised by a dynamic interplay between both systems with overlapping patterns of activation. For instance, Vossel et al. [65] characterised top-down, endogenous attention as increasing activation at bilateral FEF and IPS while suppressing activation at the right TPJ. Recent work has emphasised the significance of interhemispheric communication [37] and the existence of specific hubs to coordinate both networks, e.g., right anterior MFG, right posterior IFG, and right superior marginal gyrus [61]. There is also evidence that high connectivity between DAN and VAN nodes can improve performance during a spatial cuing task [67].

If attentional control is decomposed into endogenous and exogenous functions, which in turn, are associated with specific hubs and pathways in the brain, it is important to design studies that systematically activate top-down and bottom-up processes in order to differentiate the functional dynamics of those networks, e.g., Bressler et al., [4], Suo et al., [61], Vossel et al. [66], Wen et al. [67]. With respect to pain and cognitive demand, Seminowicz & Davis [55,54] distinguished between task-positive (i.e., inferior frontal, superior parietal, premotor, anterior insula) and task-negative (i.e., medial frontal, inferior parietal/temporal, precuneus, posterior cingulate) networks when cognitive demand and pain were simultaneously manipulated. They reported that both pain and cognitive demand increased connectivity in the task-positive network, leading to their speculation that a disruptive influence of pain on cognitive performance was due to reliance on a common network.

The objective of the current paper is to explore functional connectivity between DAN and VAN by simultaneously manipulating task demand and the presence of experimental pain. Participants played a racing game at low and high levels of difficulty with and without the cold pressor test (CPT). This type of game was selected because earlier research demonstrated increased pain tolerance when participants played a highly-demanding racing game [16]. Connectivity between cortical sites was measured using functional infrared spectroscopy (fNIRS) in combination with Multivariate Granger Causality Analysis (MVGA) [58]. fNIRS has been successfully used to capture cortical responses to experimental pain in past research [19,71]. MVGA is a useful approach for measuring network activity because directional connections between each nodes can be identified, see Wen et al [67] for example with fMRI data and Sun et al. [60] for fNIRS example.

The current study will investigate changes in functional connectivity across DAN and VAN during: (1) a comparison between a resting baseline and experimental pain induction via the CPT, and (2) a comparison between low and high difficulty game with and without the CPT. It is hypothesised that: (a) connectivity from nodes on the VAN will be enhanced in the presence of experimental pain compared to a resting baseline condition, (b) increased connectivity in the DAN will be associated with high difficulty game, and (c) VAN connectivity will be enhanced during the low-difficulty/pain condition and suppressed during the high difficulty/pain condition.

2. Method

2.1. Experimental design

The study protocol included two independent variables: (1) presence vs absence of experimental pain, and (2) low vs high level of game difficulty. The study was conducted as a within-participants design and presentation order of four different conditions was randomised.

2.2. Participants

Twenty-three participants were recruited from students and staff at our institution. This sample included 11 females and had a mean age of 24 years old (SD = 2.6 years, range = 18–34 years). Exclusion criteria for participant recruitment included pregnancy or any medical history of cardiovascular disease, diabetes, Reynaud's disease, fainting, seizures, and chronic pain. In addition, participants were asked to confirm that they were not currently experiencing any pain, taking any medication (except for the contraceptive pill), and had no fractures or open cuts/sores on their feet and ankles. The protocol for the study was approved by our institutional research ethics committee. All participants received renumeration for taking part in the study via a gift voucher worth £10/$12/11.6€.

2.3. Racing game

A racing game was created using Unity (Unity Technologies Ltd), which was presented to participants on 13″ MacBook with a 2.2 GHz Intel Core i7 processor. The participants controlled the lateral position of a vehicle from left-to-right using a joystick on a PlayStation 2 Dualshock 2 Analog Controller Gamepad. All participants except one were right-handed, so they used their right thumb to control the joystick (the left-handed participant used the left-side joystick on the Gamepad with the left thumb). The participants' vehicle was moving in the opposite direction to waves of oncoming vehicles spread across four lanes (see Fig. 1). The purpose of the game was to avoid collisions with oncoming vehicles. Participants accumulated points for every second of travel

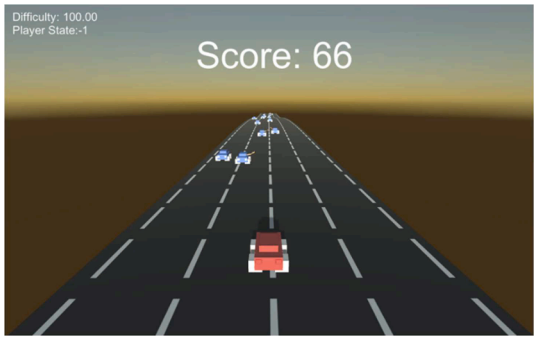

Fig. 1. Screenshot of the game used during the experimental study. Participant vehicle is red and oncoming vehicles are blue.

during which they did not collide with another vehicle and points were deducted from this total when a collision occurred; each game lasted for three minutes. The difficulty level of the game was manipulated by adjusting the speed of vehicle travel, which increased the velocity of the oncoming vehicles and the level of perceptual-motor control required to avoid collisions.

2.4. Cold pressor test

The Cold Pressor Test (CPT) is a commonly-used technique for the induction of experimental pain [64], which has been utilised in previous studies designed to investigate distraction from pain using computer games [11,16,49]. The version of the CPT used in the current protocol set the water temperature at 2 degrees Celsius with a tolerance of 0.5 degree. Participants were required to immerse the foot in a tub filled with water. This tub had two separate compartments of water separated by a permeable divider, one filled with ice to keep the water cold and a second compartment with sufficient space for participants to immerse their foot, which rested on the bottom of the tank. A digital thermometer was placed in the latter compartment to ensure that water temperature remained at the target temperature prior to and following immersion of the foot. Participants were instructed to immerse their foot to the depth of the upper part of the ankle in the cold water and to withdraw their foot when pain became unbearable. Due to the within-participants design of the study, participants were exposed to six CPT procedures during the protocol (see procedure). Participants were instructed to use alternate feet for each test (always beginning with the right foot) and successive CPT protocols were separated by at least five minutes during the procedure.

2.5. fNIRS

fNIRS data were collected using the Oxymon Mk III system (Artinis Medical Systems Ltd). The system was configured to collect six channels of fNIRS data from source-detector pairs at 10 Hz. The montage for fNIRS data collection was designed to collect data from cortical sites associated with DAN and VAN. Placement of the source-detector pairs were configured using the 10/20 System [26]. A description of the fNIRS montage is detailed in Table 1 with approximate locations for Brodmann areas derived from Okamoto et al. [40], which were used to identify different cortical sites.

2.6. fNIRS data analyses

Raw fNIRS data were initially analysed using the Homer3 toolbox [24]. The data were converted into measures of oxygenated (HbO) and deoxygenated (Hbb) haemoglobin. Given that fNIRS data would be used in combination with Granger causal connectivity analyses (GCCA), filtering was limited to a high-pass filter at 0.01 Hz, as filtering can be problematic for GCCA [56]). Due to the absence of short-channels in the montage, we were unable to deploy an optimal method to remove systemic influence on haemodynamic signals that was unrelated to neurovascular coupling [46,69]; instead we used a global regression method to remove variations that were common across multiple channels [72], even though this approach is acknowledged to a blunt method for signal correction [45]. In this case, median values were calculated for HbO and Hbb across all six channels, regressed against each channel, and the raw residuals retained. These values were standardised using a z-score procedure and an oxygenation score calculated for each channel by subtracting Hbb from HbO.

Table 1
Description of six-channel fNIRS montage used in the study. Note: FEF = Frontal Eye Field, IFG = Inferior Frontal Gyrus, IPS = Intraparietal Sulcus, TPJ = Temporoparietal Junction.

Channel/Node	Source	Detector	Brodmann	Cortical site	DAN/VAN
1	F3	F1	8	Left FEF	DAN
2	F4	F2	8	Right FEF	DAN
3	FC8	F8	45	Right IFG	VAN
4	P1	CP1	7	Left IPS	DAN
5	P2	CP2	7	Right IPS	DAN
6	P6	P8	39	Right TPJ	VAN

The GCCA analyses was conducted using functions from the Multivariate Granger Causality Analysis (MVGC) toolbox [3,56] using MATLAB R2020b (Mathworks Inc.). The MVGC toolbox implements a statistical interpretation of Granger-causality in which including the past values of channel *a* leads to better prediction of channel *b* than using past values of channel *a* alone [58]. The functions included in the MVGC toolbox achieve this implementation via vector autoregressive modelling (MVAR) that predicts a given time series as the weighted sum of past values.

A Granger analysis was created in MATLAB using functions obtained from the MVGC toolbox, which modelled G-causality across a 5 s epoch of oxygenation data from all six available channels. Prior to modelling, the oxygenation data for each channel were detrended (i.e., best-fitting line removed from each time series), demeaned (i.e., removal of temporal mean), and differenced (i.e., first-order differencing); all these steps were performed to maximise the probability of creating time series that exhibited covariance stationary, which is a prerequisite for GCCA. Each epoch was subjected to a formal test of stationary called the KPSS test [30] using a bespoke function from MVGC [57]. For the results of GCCA to be valid, it is also important to verify that the MVAR adequately captures the data under analysis and our analyses incorporated three functions from the MVGC toolbox to test this assumption: (1) the Durbin-Watson test [13] that tests whether the residuals from the MVAR are serially uncorrelated, (2) the consistency test [12] that assesses the percentage of the data captured by the MVAR model, and (3) the adjusted sum-square error of the regression – see Seth [57] for details. The Bayesian/Schwartz criterion was used to select the best model order to use, i.e., the number of past observations to incorporate into the MVAR. The precise model order varied for each epoch of data analyses, the range of model orders was 4–8.

Therefore, a series of tests were conducted on each epoch to test assumptions associated with GCCA and epochs were excluded from analyses if: (a) KPSS test was significant at $p < .01$, (b) the Durbin-Watson test was significant at $p < .01$, (c) the consistency of the data fell below 80 %, and (d) if the adjusted sum square error for 2 channels or more was less than 0.3 [3,57]. These criteria led to an average of 18.4 % of all available epochs being rejected for GCCA analyses across all data collected during the study (of which a sub-set was retained for statistical analyses, see details later in this section). The resulting GCCA yielded three groups of metrics for each epoch of data, these were:

(1) Node causal density – an index of the dynamic complexity for each node in the network, i.e., if a node has high causal density, this indicates that it functions as a hub of dynamic complexity [57]
(2) Node causal flow – if the GCCA identifies a significant pathway between two nodes, this pathway has a direction, e.g., node 1 connects to nodes 2 and 3 but only node 2 connects to node 1. In this case, node 1 has two out-degrees (pathways to other nodes) and one in-degree (pathways from other nodes). Node causal flow represents the difference between the number of out-degrees and in-degrees for each node. High causal flow indicates that the node functions as a causal 'source' with a greater number of out-degrees than in-degrees. If the causal flow is negative, this may indicate that this node functions as a causal 'sink' in the network [57].
(3) Conditional G-causality – every possible pathway in the network is associated with a magnitude of G-causality interaction, which can be quantified as the log ratio of prediction errors. A higher

number means a greater level of G-causality for a directional pathway between two nodes.

This GCCA pipeline was applied to two comparisons between conditions in the current experiment. The first applied GCCA to a comparison between an eyes-open, resting baseline (3 min duration) and a CPT. The GCCA was applied only to the four final 5 s epochs of the CPT before the participant withdrew his or her foot from the cold water to target this analysis on a time epoch when pain would be maximal. In order to omit the effects of movement and movement preparation, the final 5 s epoch of the CPT was removed from this analysis and only three 5 s epochs were retained for statistical testing. Two participants did not keep their feet in the water for longer than 15 s and both were excluded from this analysis. The metrics associated with the GCCA were compared to a 15 s period of the eyes-open, resting baseline that occurred 30 s before the end of the baseline condition.

The second analysis applied GCCA to compare four different conditions that varied with respect to game difficulty and the presence of pain, these were: low-difficulty game only, high-difficulty game only, low-difficulty game with CPT, and high-difficulty game with CPT. For these analyses, we used the same approach as the previous comparison, a 15 s period was identified prior to participants removing their foot from the cold water while playing the game, which was compared to the same 15 s period in the game only condition. As in the previous analysis, two participants were excluded because they removed their foot from the cold water in a period shorter than 15 s.

2.7. Behavioural/subjective measures

The CPT yielded a behavioural measure of pain tolerance, i.e., duration that the foot was immersed in cold water, and these data were recorded. Two subjective questionnaires were administered to participants after they played the game at both levels of difficulty as a manipulation check, these were: the NASA-Task Load Index [22] and the Motivation questionnaire derived from the Dundee Stress State Questionnaire [35].

2.8. Procedure

The participant arrived at the laboratory and read an information sheet that described the experimental protocol, they had an opportunity to ask questions of the experimenter before providing written consent. The first step of the procedure was to introduce participants to the CPT; therefore, the participants were asked to place their foot in the cold water and a CPT was conducted purely as a familiarisation exercise (i.e., no data were collected). During the second stage of the procedure, the fNIRS headcap was fitted to the participant. Once the experimenter was satisfied with signal quality, the participant was introduced to the game and provided with a short (2 min) period of familiarisation with the joystick control.

The next stage of the procedure was for the participants to perform an eyes-open, resting baseline condition for 3 min. After the baseline procedure, participants performed a CPT and their fNIRS/behavioural data were recorded. Participants were subsequently exposed to four conditions (low-difficulty game, high-difficulty game, low-difficulty + CPT, high-difficulty + CPT), presented in randomised order. After each condition, the participants had approximately 5 min to complete the post-condition questionnaires. The foot that was submerged in the cold water was alternated for each administration of the CPT. Upon completion of the final condition, the fNIRS apparatus was removed and the participant was thanked, debriefed, and received their renumeration.

3. Results

3.1. Subjective and behavioural data

Analyses of subjective data were performed as a manipulation check on the game difficulty manipulation. A 2 (game difficulty) × 2 (TLX, Motivation) MANOVA was performed on the subjective data using SPSS v28 (as were all statistical tests of significance reported in this section). This model revealed a significant effect for game difficulty [$\Lambda(1,21) = 0.34$, $p < .01$, $\eta^2 = 0.66$]. Post-hoc tests confirmed that subjective mental workload and motivation both significantly increased during high-difficulty compared to low-difficulty gaming; descriptive statistics are presented in Table 2.

A univariate ANOVA was conducted to analyse pain tolerance data from the CPT, i.e., how long participants kept their foot in the cold water. This analysis revealed a significant main effect [$F(2,20) = 7.40$, $p < .01$, $\eta^2 = 0.43$]. Pairwise comparisons revealed that participants kept the foot in the water for a significantly longer period when playing the game compared to the baseline period where no game was present, however, there was no significant difference in immersion times between the low- and high-difficulty game conditions. Descriptive statistics are presented in Table 2.

3.2. Analysis 1: Effects of cold pressor test on functional connectivity

A 2 (baseline vs CPT) × 6 (nodes) ANOVA was performed on the measure of causal density per node in the network, but this model failed to reveal significant main effects for either condition [$F(1,20) = 0.12$, $p = .73$], node [$F(1,20) = 1.43$, $p = .27$] or any interaction effect. Descriptive statistics for causal density per node are reported in Table 1a of the supplementary material. The same model was applied to measures of causal flow per node, but no significant effects were found for condition [$F(1,20) = 2.33$, $p = .14$], node [$F(1,20) = 0.49$, $p = .78$] or the interaction effect (see Table 1a of supplementary material for descriptive statistics).

A measure of G-causality was generated for every pathway in the network using each node as the origin point and the other five channels/nodes as destination points (see Table 1). This metric was analysed via a series of 2 (baseline vs CPT) × 5 (destination node) ANOVAs, performed separately on each node in the network. The results from these ANOVAs are presented in Table 3.

A chord diagram (Fig. 2) was produced to illustrate significant main effects of condition at RIFG, LIPS and RIPS and the interaction effect at RTPJ on G-causality. In the chord diagram, differences in G-causality have been converted into *t*-values, where a positive value indicates increased G-causality during CPT compared to resting baseline; *t*-values of 2.2 and above are significant at $p < .01$ with Bonferroni adjustment. Fig. 2 illustrates a significant increase in G-causality from LIPS, RIPS and RTPJ to the RFEF during the CPT; we also observed increased G-causality from RIFG and RTPJ to the LFEF node.

3.3. Analysis 2: Effects of game difficulty and CPT on functional connectivity

A 2 (pain: no-CPT/CPT) × 2 (game difficulty: high/low) × 6 (node)

Table 2
Descriptive statistics for subjective and behavioural data (N = 21).

	Baseline	Low Difficulty	High Difficulty
Task Load Index		2.81	5.45
		[0.83]	[1.42]
Motivation		35.74	41.37
		[3.81]	[3.62]
Cold Pressor Times (s)	38.23	68.95	72.64
	[32.63]	[60.59]	[66.39]

Table 3
ANOVA results for resting baseline vs cold pressor test comparison. Note: LFEF = Left Frontal Eye Field, RFEF = Right Frontal Eye Field, RIFG = Right Inferior Frontal Gyrus, LIPS = Left Intraparietal Sulcus, RIPS = Right Intraparietal Sulcus, RTPJ = Right Temporoparietal Junction. η^2 only reported for results at p <.05 and significant effects are given in italics.

	Condition (main)			Node (main)			Interaction		
	F	p	η^2	F	p	η^2	F	p	η^2
LFEF	1.71	0.21		1.14	0.38		1.33	0.30	
RFEF	1.67	0.22		1.08	0.40		0.98	0.45	
RIFG	*11.79*	*<0.01*	*0.38*	1.19	0.35		0.69	0.61	
LIPS	*5.16*	*0.04*	*0.22*	2.76	0.06		0.77	0.56	
RIPS	*6.54*	*0.02*	*0.26*	0.17	0.95		0.29	0.88	
RTPJ	2.71	0.12		0.49			*2.54*	*0.05*	*0.12*

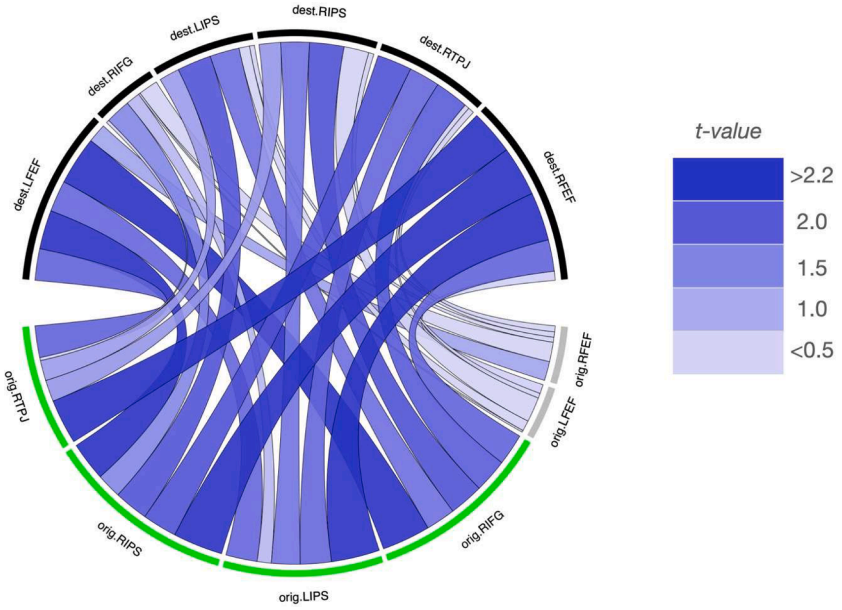

Fig. 2. Chord diagram illustrating main effect of condition (Cold Pressor Test minus Baseline) on Granger causality for all pathways in the network. The origin (orig.) of the pathway is represented by the lower half of the circle with destination (dest.) provided in top half. Positive *t*-values = higher G-causality for those pathways in the CPT condition compared to baseline. Origin nodes illustrated in green indicate the presence of a significant effect in the ANOVA model (Table 3).

ANOVA was conducted on the causal density metric for each node. This analysis revealed a significant main effect for pain [F(1,21) = 10.01, p <.01, η^2 = 0.32]; pairwise comparisons indicated that mean causal density was higher when participants played the game while experiencing the CPT [M = 0.974, SE = 0.015] compared to playing the game in the no-CPT condition [M = 0.893, SE = 0.015]. However, there was no significant effect for either game difficulty [F(1,21) = 0.30, p =.58] or node [F(5,17) = 0.93, p =.49] and none of the interaction effects reached statistical significance. Descriptive statistics for causal density per node are presented in Table 2a of the supplementary material. The same ANOVA model was used to analyse causal flow per node, but this analysis failed to reveal significant main effects for pain [F(1,21) = 0.91, p =.35], game difficulty [F(1,21) = 3.35, p =.08] or node [F(5,17) = 1.61, p =.21], and there were no significant interactions. Descriptive statistics for causal flow per node are presented in Table 2a of the supplementary material.

A series of 2 (pain/no pain) × 2 (high/low game difficulty) × 5 (destination node) ANOVAs were conducted on the measure of G-causality for each node on the network. The results from these ANOVAs are presented in Table 4. Note that F values for interactions are only included if the interaction is significant at p <.05.

Chord diagrams were created to illustrate the magnitude of Granger causality for all paths. The ANOVA analyses (Table 4) revealed one significant main effect for pain and number of significant interaction effects. Fig. 3a represents differences in G-causality (represented by *t*-values) between gameplay with CPT compared to gameplay only, i.e.,

Table 4
ANOVA results for 2 (pain) × 2 (game demand) × 5 (node) model for each node. Note: η^2 only reported for results at p <.05 and significant effects in italics.

	Pain (P)			Difficulty (D)			Node (N)			Interactions			
	F	p	η^2	F	p	η^2	F	p	η^2		F	p	η^2
LFEF	2.79	0.11		0.31	0.58		0.55	0.70		*D * N*	*4.04*	*0.02*	*0.49*
RFEF	*4.41*	*0.05*	*0.18*	1.31	0.26		1.05	0.41					
RIFG	1.85	0.19		2.46	0.13		0.92	0.47		*P * D*	*8.44*	*<0.01*	*0.30*
LIPS	2.69	0.11		1.36	0.26		0.08	0.98		*P * D*	*8.76*	*<0.01*	*0.30*
										*D * N*	*2.91*	*0.05*	*0.41*
RIPS	1.00	0.33		0.32	0.58		1.58	0.22					
RTPJ	1.26	0.27		0.66	0.43		0.14	0.96		*P * D*	*8.24*	*0.01*	*0.30*

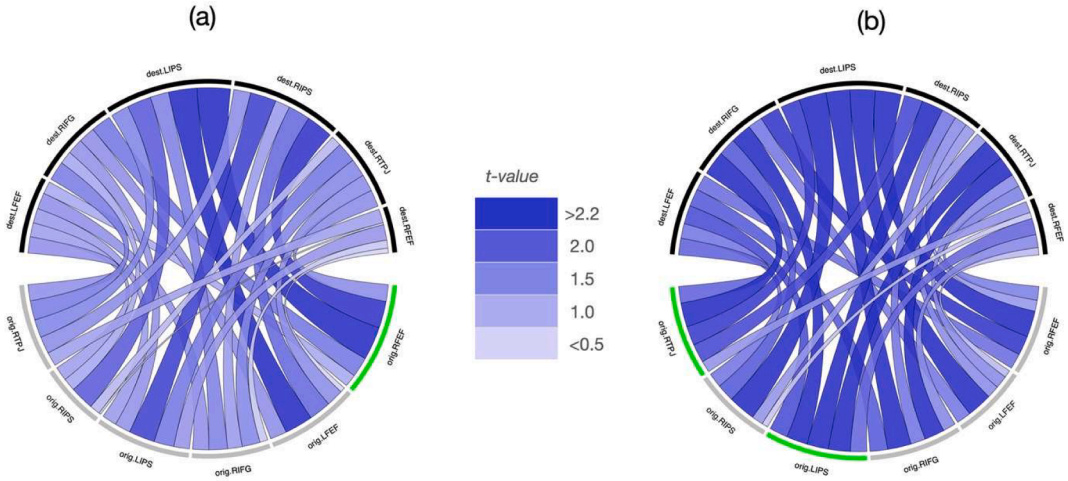

Fig. 3. Chord diagram illustrating main effect of Pain during gameplay (a) and specifically the effect of Pain during the High-Difficulty game (b) on Granger causality for all pathways in the network. Positive values = increased G-causality in the presence of pain. The origin of the pathway is represented by the lower half of the circle with destination provided in top half. Origin nodes illustrated in green indicate significant effect in the ANOVA model (see Table 4).

higher *t*-value = higher G-causality during gameplay with CPT. Fig. 3a illustrates that G-causality was significantly higher from LFEF to LIPS and from RFEF to LIPS when participants played the game while experiencing pain from the CPT.

Fig. 3b provides an illustration of significant interactions between pain and game difficulty; in this case, differences in G-causality between CPT and no-CPT conditions are presented for the high-difficulty game only, i.e., higher *t*-value = increased G-causality while playing the high difficulty game with the CPT compared to playing the high difficulty game without CPT. In this case, we observed increased G-causality from LIPS to RIFG, RTPJ and RIPS. We also found significant increase in G-causality from: RTPJ to RIFG, RIPS to LIPS, RIFG to LIPS and RTPJ, LFEF to LIPS, and RFEF to LIPS.

Fig. 4 is identical to Fig. 3 but represents changes in G-causality due to game difficulty as a main effect (a), and as an interaction effect (b). In both Fig. 4a and 4b, a higher *t*-value should be interpreted as increased G-causality during high game difficulty compared to low game difficulty; Fig. 4b represents this contrast when participants also experienced the CPT. Fig. 4a illustrates two significant G-causality for two pathways: from LFEF to LIPS, and from RIFG to LIPS. In the case of Fig. 4b, we observed a significant increase of G-causality from TPJ to LFEF and from LIPS to LFEF, there were significant increases observed from RIFG to LFEF and LIPS, and from RFEF to LFEF.

4. Discussion

It was expected that connectivity at the two sites associated with the VAN would increase in the presence of experimental pain. We also anticipated that connectivity across sites associate with the DAN would be enhanced in response to increased game demand. The former hypothesis was explored via three analyses, by measuring connectivity: (a) during CPT compared to resting baseline, (b) during CPT in combination with gameplay (regardless of difficulty level) compared to gameplay only, and (c) during CPT in combination with high difficulty game compared to high difficulty game only (Fig. 5). The latter hypothesis was investigated via an analysis of connectivity during: (a) high difficulty game vs low difficulty game in the absence of experimental pain, and (b) high difficulty game vs low difficulty game in the presence of experimental pain (Fig. 6). All five contrasts are summarised in Figs. 5 and 6, where only pathways that achieved statistical significance on the t-tests (Figs. 2, 3 and 4) are reproduced in a schematic form.

In the case of Fig. 5a, we find support for our hypothesis; three of the five significant pathways originate from the right IFG and TPJ. This observed pattern of bottom-up G-causality supports the model

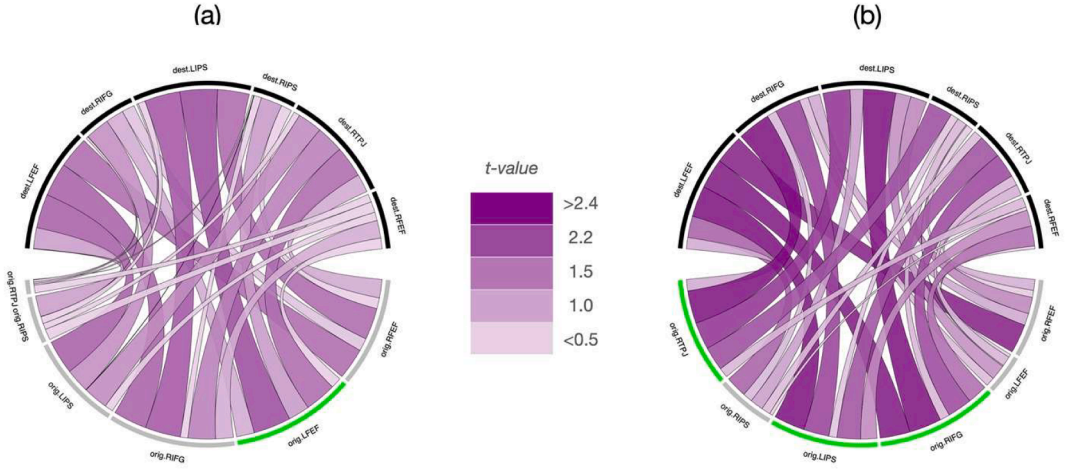

Fig. 4. Chord diagram illustrating main effect of Game Difficulty as a main effect (a) and as an interaction (b) when participants also experienced the CPT. Positive values = higher G-causality due to high difficulty compared to low difficulty game. The origin of the pathway is represented by the lower half of the circle with destination provided in top half. Origin nodes illustrated in green indicate significant effect in the ANOVA model (see Table 4).

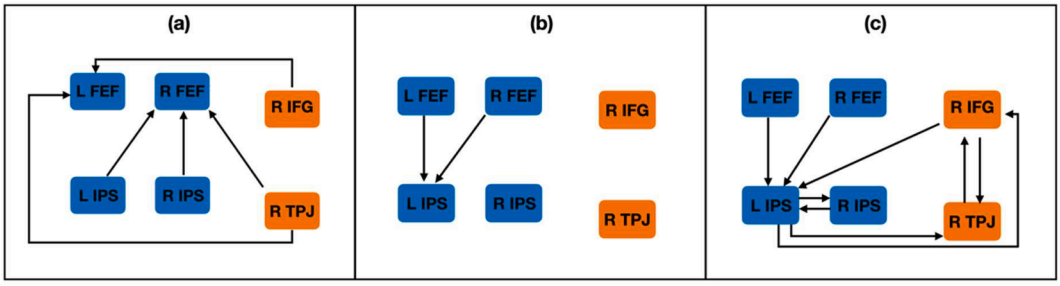

Fig. 5. Schematic representation of directional pathways where a significant increase in G-causality was found due to introduction of experimental pain for: (a) cold pressor test only, (b) cold pressor test while playing the game, and (c) cold pressor test while playing the high difficulty game. Nodes associated with DAN in blue, nodes associated with VAN in orange.

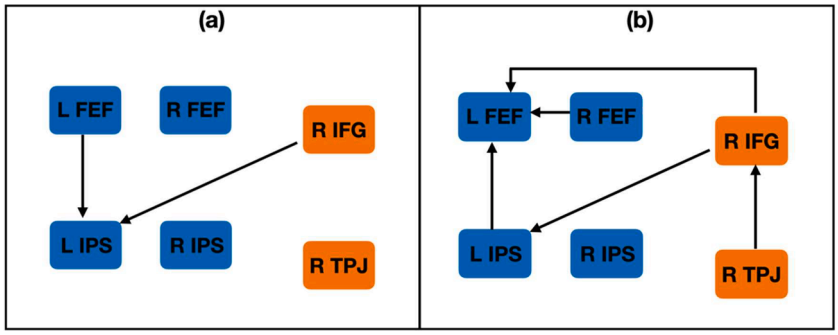

Fig. 6. Schematic representation of directional pathways showing a significant increase in G-causality due to increased game difficulty for: (a) playing game only, and (b) playing game in combination with cold pressor test. Nodes associated with DAN in blue, nodes associated with VAN in orange.

developed by Legrain et al. [32] and summarised by Torta et al. [62], wherein attention is captured involuntarily by salient painful stimulation via a number of bottom-up pathways. However, when the CPT is combined with playing the racing game, we observed two top-down pathways from both frontal sites to the left IPS (Fig. 5b). This pattern suggests increased activation in the DAN to reinforce attention to task-related goals in the presence of painful sensation. This resulting pattern supports the findings reported by Seminowicz & Davis [55,54] where activity in their 'task-positive network' was increased by the presence of experimental pain. There is also evidence that greater G-causality from FEF to IPS is associated with an enhancement of performance during a spatial visual attention task [67].

When high level of game difficulty is combined with experimental pain, we would anticipate both DAN and VAN to be activated. In Fig. 5 (c), we observed the same top-down pathways shown in Fig. 5(b) but this pattern is supplemented by the right IFG. The involvement of the right IFG may be significant because the latter may function as a connecting hub between DAN and VAN [8,9,61]. Fig. 5c is also characterised by bidirectional pathways between the TPJ and IFG in the right hemisphere, which may indicate a strengthening of bottom-up 'interuptive' pathways that direct attention to pain as top-down attention has been fully engaged by a highly demanding game [32,62]. Fig. 5c also revealed the left IPS to be the most significant hub of activity, acting as a destination for top-down, interhemispheric pathways and serving as source for bottom-up pathways to the right hemisphere. There is evidence of the left IPS serving a pivotal role in the coordination of DAN and VAN during a study of visual attention span [73], and while some have focused on connectivity in the right hemisphere between IPS and TPJ [67], others have argued for greater consideration of left hemispheric areas as potential nodes and hubs in the DAN/VAN dichotomy [37,66]. In our case, it is important to note that our participants were right-handed and used the right thumb to play the game, hence it is possible that the prominence of the left IPS during high difficulty gaming resulted from contralateral activation.

The second part of the analyses focused on the effect of game difficulty on G-causality (Fig. 4) with an assumption that greater top-down connectivity within the DAN network would be strengthened as game difficulty increased. The main effect of game difficulty is illustrated in Fig. 6a where we observed top-down influences from the left FEF and right IFG on the left IPS. This pattern confirms the results from previous studies [7,20,66,67] and importance of frontoparietal connectivity for attentional functions, such as alertness [43] and orientation [18]. The pathway from the right IFG to IPS was unexpected, but reinforces the point made earlier about the potential importance of right IFG as a connecting hub between DAN and VAN [61]. When low and high levels of game difficulty were contrasted in combination with the CPT (Fig. 6b), we observed a number of differences from our main effect: (1) the pathway between left FEF and IPS is bottom-up as opposed to top-down, (2) there is a bottom-up pathway from the right TPJ to the right IFG, which connects with the left FEF, and (3) an interhemispheric right-left path between both FEF nodes. These patterns provide evidence for bottom-up influences (1 and 2) when experimental pain is maximised [62] with destination nodes on the left hemisphere, presumably due to contralateral activation as participants play the game using the right thumb. An increase of interhemispheric connectivity between both frontal sites has also been observed during the top-down attention using direct causal modelling [66].

To summarise, we observed increased G-causality from the left FEF and right IFG to left IPS when contrasting the effects of pain (Fig. 5c) and increased game difficulty (Fig. 6a and b). As increased connectivity via both pathways was common to both experimental manipulations, this finding suggests either a common attentional strategy in response to increased game difficulty and pain or convergence of connectivity based on a more foundational concept, such as arousal [55,54]. A combination of experimental pain with high game difficulty was associated with increased G-causality between VAN nodes in the right hemisphere and between DAN and VAN nodes (Fig. 5c and 6b). This pattern may reflect a combined influence of painful stimulation with high difficulty gaming, i.

e., bottom-up pathways from the VAN must be highly activated in order to exert their interruptive influence on top-down, goal-focused attention [32,34]. We observed the left IPS playing a particularly prominent role in the network with respect to experimental pain (Fig. 5c). When contrasting high vs low game difficulty in combination with the CPT, we found an interhemispheric pathways that ran in a bottom-up fashion from VAN nodes to influence activation at the left FEF, which is consistent with the prioritization of painful stimulation described by Torta et al. [62].

The methodology of the study was limited by several factors. The use of the CPT was problematic due to a lack of sensitivity to the game demand manipulation and the related issue of high individual variability (Table 2). Our approach was to curtail our analyses of fNIRS connectivity to the 15 s period of the CPT that preceded removal of the foot from the cold water, this decision assumed that painful sensation would be maximal and consistent across all participants at that point, but this presumption of equivalence is questionable given the great variability in cold pressor times (Table 2). Given that increasing game difficulty has been found to reliably increase pain tolerance using the CPT [16], the absence of any such effect in the current study raises questions about the design and impact of the racing game. While subjective data indicated increased mental workload and motivation during high difficulty gaming (Table 2), with the benefit of hindsight, we would question whether the demands of the game were sufficiently cognitive in nature to permit comparison with existing literature. The primary factor influencing game difficulty in the current study was time pressure, which tested the perceptual-motor skills and reaction times from participants. With respect to the fNIRS, as stated in the Method section, the absence of short-channels was a significant constraint on our protocol. While fNIRS offers a method of neuroimaging that permits testing under naturalistic conditions, there were concerns about the accuracy of an optode placement system that relied solely on the 10/20 system. For a sparse network that designed to represent key sites, the 10/20 system offers, at best, an approximation of spatial fidelity with respect to Brodmann sites (Table 1). There are techniques available that permit registration of scalp-mounted sensors with much greater fidelity and personalisation, such photogrammetry [23,36] and the use of a digitizer [68].

The study was designed to minimise the fNIRS montage and specifically target those cortical areas associated with DAN and VAN by earlier research (e.g., [8]. However, this decision introduces ambiguity into the interpretation of our results. For example, if we report evidence for increased top-down connectivity between frontal and parietal sites when participants played the game while experiencing pain (Fig. 5b), does this effect reflect activation across the DAN? Or is this effect merely a sub-component of another, larger network that is unrepresented in our analyses due to the sparsity of our fNIRS montage? The decision to target a small number of specific cortical sites makes it impossible to present our significant findings in the context of cortical networks in a broader context.

Therefore, the results of the study should be treated as preliminary and are subject to replication. For example, a series of experiments could be conducted across a range of cognitive tasks, where the level of challenge and severity of pain are simultaneously and systematically manipulated. By comparing the resulting impact on a network that encompassed both DAN and VAN nodes, we could delineate changes in G-causality in a more rigorous fashion than the current study. It would be ideal to reproduce the experiment with a high-density fNIRS system with greater coverage of the cortex that would permit interpretation in a broader context of cortical networks, as well as improving spatial registration and data fidelity, e.g., Frijia et al. [21]. If the results of the current study can be replicated, it would be interesting to explore individual differences in network dynamics for DAN and VAN when exposed to experimental pain during gaming, e.g., chronic pain sufferers, experienced gamers.

To summarise, this study provides preliminary data using Granger causality that was generally supportive of the top-down/bottom-up model used to describe the interaction of cognitive demand and pain [32,62], which is based on the DAN/VAN model described by Corbetta et al [8]. We also found some evidence for interhemispheric pathways [37,61] that may be significant for coordination of DAN and VAN when competition between endogenous and exogenous stimuli is particularly acute.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neulet.2022.136967.

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