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The role of the dorsal Anterior Cingulate Cortex (dACC) in a cognitive and emotional counting Stroop task: Two cases

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Abstract.
Background: The anterior cingulate cortex (ACC) has been implicated in both cognitive and emotional processing, with cognitive information proposed to be processed through the dorsal/caudal ACC and emotional information through the rostral/ventral ACC.
Objective: The objective of this study is to investigate the role of the dorsal anterior cingulate cortex (dACC) in cognitive and emotional processing using a cognitive and emotional counting Stroop task in two patients in whom abnormalities in the dACC were identified and treated.
Methods: Two patients performed the cognitive and emotional counting Stroop task before and after treatment to examine whether the dACC has a specific or more general processing function.
Results: We observed an overall improvement in the emotional, cognitive, and neutral trials of the counting Stroop task after the intervention, indicating that the dACC is not a subregion of the ACC that only contributes to a specific domain.
Conclusion: This study reveals that the dACC is not just a subregion of the ACC that contributes to a specific cognitive function, but is rather part of a salience network that influences general brain functioning, influencing cognitive as well as emotional processing.

Keywords: Anterior cingulate cortex, Stroop task, brain calcification, invasive brain stimulation, non-invasive brain stimulation

1. Introduction

The anterior cingulate cortex (ACC) has been found to be an important brain area engaged in emotional as well as cognitive processes (Bush, Luu, & Posner, 2000; Davis et al., 2005). Neuroimaging studies have demonstrated dysfunctional ACC activity in many neuropsychiatric disorders, and the success of bilateral cingulotomy psychosurgery in relieving psychiatric symptoms has revealed a role of the ACC in the regulation of emotional behavior (Gasquoine, 2013). This is also supported by structural imaging studies: in a conjunction analysis of voxel based morphometry, meta-analytic studies of axis 1 psychiatric pathologies (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety) have demonstrated that the dorsal anterior cingulate cortex (dACC) and insula, i.e. the core of the salience network (Seeley et al., 2007), were commonly involved in all of the abovementioned mental disorders. Increased activity in the ACC has also been found during a variety of cognitive

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tasks in healthy subjects including divided attention, verbal fluency, novelty detection, working memory, and, most notably, the Stroop task (Bush et al., 1998; Carter, Mintun, & Cohen, 1995; Pardo, Pardo, Janer, & Raichle, 1990; Swick & Jovanovic, 2002).

The ACC has been purported to be part of a circuit involved in a form of attention that serves to regulate both cognitive and emotional processing, with cognitive information processed through the dorsal/caudal ACC and emotional information through the rostral/ventral ACC (Bush et al., 2000). However, this has not been confirmed by all meta-analytic studies. Some studies demonstrate that the dACC is involved in cognitive, affective, sensory, and autonomic processing (Beissner, Meissner, Bar, & Napadow, 2013; Legrain, Iannetti, Plaghki, & Mouraux, 2011; Miller et al., 2001), suggesting a more general function for the dACC, such as salience processing (Legrain et al., 2011; Seeley et al., 2007). The dACC, as part of the salience network, has been suggested to have a central role in the detection of behaviorally relevant (i.e. "salient") stimuli and the coordination of neural responses (Uddin, 2015). The term 'salient' describes a stimulus or an aspect of a stimulus that stands out from its counterparts (Uddin, 2015).

Two versions of the counting Stroop task, one involving cognitive interference (cognitive counting Stroop) and the other involving emotional interference (emotional counting Stroop), have been shown to engage two ACC subdivisions differentially (Bush et al., 2000; 1998; Whalen et al., 1998). The cognitive counting Stroop task activates the caudal/dorsal ACC (Bush et al., 2000; 1998) while the emotional counting Stroop task activates the rostral/ventral ACC in healthy subjects (Bush et al., 2000; Whalen et al., 1998). Moreover, reciprocal suppression of the affective subdivision during cognitive tasks has often been observed, as well as reciprocal suppression of the cognitive subdivision during intense emotional states (Bench et al., 1992; Bush et al., 1999; 2000; Drevets & Raichle, 1998; Mayberg, 1997). However, this concept of the role of the two subdivisions of the ACC in the processing underlying the cognitive and emotional counting Stroop task is mostly based on findings generated by neuro-imaging techniques (Bush et al., 2000).

Subsequent research has focused on non-invasive brain stimulation as an interference technique in order to complement findings from imaging studies. This permitted researchers to attribute a causal involvement of the dACC on performance in the cognitive counting Stroop task. Hayward and his colleagues (2004, 2007) used high-frequency (HF) double-cone coil transcranial magnetic stimulation (TMS), which has been shown to be able to modulate ACC activity (Harmer, Thilo, Rothwell, & Goodwin, 2001; Hayward et al., 2007), during the counting Stroop task and eliminated the Stroop effect (i.e. improved the performance on the Stroop task) when targeting the dorsal part of the ACC (1.5 cm anterior to 1/3 distance from nasion-inion) in healthy subjects (Hayward, Goodwin, & Harmer, 2004; Hayward et al., 2007). In their positron emission tomography (PET) study, they further showed that medial frontal TMS (targeting the dACC) administered during the counting Stroop task resulted in increased activity in the dorsal part of the ACC and decreased the activity in the more ventral part (affective subdivision) of the ACC (Hayward et al., 2007). These findings support the idea of cognitive and affective divisions of the ACC that appear to be inversely connected, as stimulating the dACC while engaging in a cognitive task reduced the activity of the more ventral part of the ACC (Bush et al., 2000). However, more information is needed regarding the role of the dACC in emotional processing to investigate any cognitive-emotional interactions as an emotional counting Stroop task was not administered in those studies. The dACC has deliberately been targeted in lesioning (i.e. cingulotomy psychosurgery) and neuromodulator techniques (e.g. deep brain stimulation, TMS) for the treatment of various disorders including obsessive-compulsive disorders, pain, addiction, and tinnitus (e.g. (Brown et al., 2016; Bush et al., 1999; De Ridder, Joos, & Vanneste, 2016; De Ridder, Leong, Manning, Vanneste, & Glue, 2017; De Ridder, Manning, et al., 2016; De Ridder, Vanneste, Kovacs, Sunaert, & Dom, 2011; Russo & Sheth, 2015; Tzabazis et al., 2013)), pointing to a more general role of the dACC than involvement in cognitive processing alone. Moreover, the dACC as part of the 'salience network' has been identified as the 'psychiatric core' or one of the core brain regions affected across most psychiatric disorders (Downar, Blumberger, & Daskalakis, 2016; Goodkind et al., 2015). Furthermore, an electrophysiological study at the single-cell level investigating the dorsal/caudal ACC neurons during a cognitive and emotional counting Stroop task in obsessive-compulsive disordered patients suggested that the dorsal/caudal ACC contains some neurons that respond differently to high-conflict words that are emotionally laden (i.e. emotional words e.g. 'torture') but not to high contrast words without emotional valence (i.e.

incongruent cognitive words, e.g. four times the word one presented) (Davis et al., 2005). This suggests that the dorsal/caudal ACC may not be functionally exclusive and may contribute to more general processing purposes than only cognitive processing (Davis et al., 2005), complementary to some functional imaging studies (Beissner et al., 2013).

In this study, we investigate two patients who underwent surgery modulating the dACC to provide a better understanding of the role of the dACC in the performance of a cognitive and emotional counting Stroop task. Each patient had an abnormality at the dACC which was treated in different ways: (1) by the excision of the calcification of cerebral falx (i.e. falx ossification) impinging on the dACC and (2) by modulating activity in the dACC using bilateral (dACC) cortical stimulation by means of implanted paddle electrodes. Both patients are authoritative cases to study the role of the dACC in both emotional and cognitive functioning because their dysfunction is limited to the dACC. In the first subject, the falx calcification was limited to the dACC and surgically removed and in the second subject, the changed neuronal activity was only seen in the dACC. By using an invasive neuromodulation technique (implanted electrodes) on the second subject, stimulation was more selective than it would be through non-invasive neuromodulation techniques such as double-cone coil TMS. We hypothesize that in both patients, targeting the dACC will result in improved performance in processing of the cognitive and emotional counting Stroop task, thereby supporting a more general role of the dACC.

2. Methods

2.1. Participants

2.1.1. Case study 1

A 48-year old tinnitus patient presented to the multidisciplinary Tinnitus Research Initiative Clinic at BRAI2N Neuromodulation Center at Antwerp University, Belgium. He suffered from bilateral polyphonic tinnitus, perceived as a combination of a low and high pure tone on the left and a hum on the right, which persisted for 1 year and developed after a whiplash injury. This is associated with what the patient describes as emotional instability, with rapidly fluctuating emotional outbursts. He scored 10/10 on a numeric rating scale (NRS) for both tinnitus loudness and distress and was diagnosed as a grade 2 tinnitus (= moderate) based on a validated translation (Meeus, Blaivie, & Van de Heyning, 2007) of the tinnitus questionnaire (Goebel & Hiller, 1994). His tinnitus was not influenced by stress or fatigue, and was not associated with cryptogenic hemifacial spasm, geniculate neuralgia, or optogenetic vertigo. A CT and MRI demonstrated a calcified meningioma of the right falx, impinging on the dACC, extending into the Supplementary Motor Area (SMA), predominantly on the right (Fig. 1). The fMRI also showed hyperactivity at the dorsal anterior cingulate cortex (Fig. 2). He was resistant to treatment by sipralexa, melitracen 10 mg + flupentixol 0.5 mg, clonazepam 1 mg, naltrexone 5 mg, Inderal 10 mg, clonidine, depakene, and androcur (which he took for gender dysphoria).

After resection of the calcified meningioma (Fig. 1) the patient reported improvement to a score of 3/10 for the left-sided tinnitus loudness on the NRS and a dramatic improvement in his emotional instability. His right-sided hum did not benefit from the resection but could be controlled by ½ tablet of zolpidem. MRI after surgery showed a clean resection of the calcified meningioma (Fig. 1) as well as reduced activity in the dorsal anterior cingulate cortex when presented with the tinnitus-matched tone (Fig. 2).

2.1.2. Case study 2

A 64-year old tinnitus patient presented to the multidisciplinary Tinnitus Research Initiative Clinic at BRAI2N Neuromodulation Center at Antwerp University, Belgium. He suffered from bilateral tinnitus, which persisted for 39 years. The tinnitus was perceived as pure tone, somewhat more pronounced in the left than the right. He scored 10/10 on a numeric rating scale (NRS) for both tinnitus loudness and distress and reported this to get even worse with fatigue, stress, and noise exposure. He also suffered from hyperacousis (sound intolerance) associated with high-frequency hearing loss compatible with presbycusis. Some imbalance disorder was reported in the form of a drunken feeling with a slight deviation to the right. The patient denied headaches and has no neck pain that modulated the tinnitus. There were no other signs of somatosensory modulation of his tinnitus. He experienced neither overt or covert hemifacial spasms nor geniculate neuralgia. His Tinnitus Questionnaire (TQ) (Goebel & Hiller, 1994) score was 68 out of 84, i.e. grade IV, psychologically decompensated tinnitus. His Hospital Anxiety and Depression scale (HADS) scores for anxiety and depression were 13 for both anxiety (13/21) and depression (13/21).

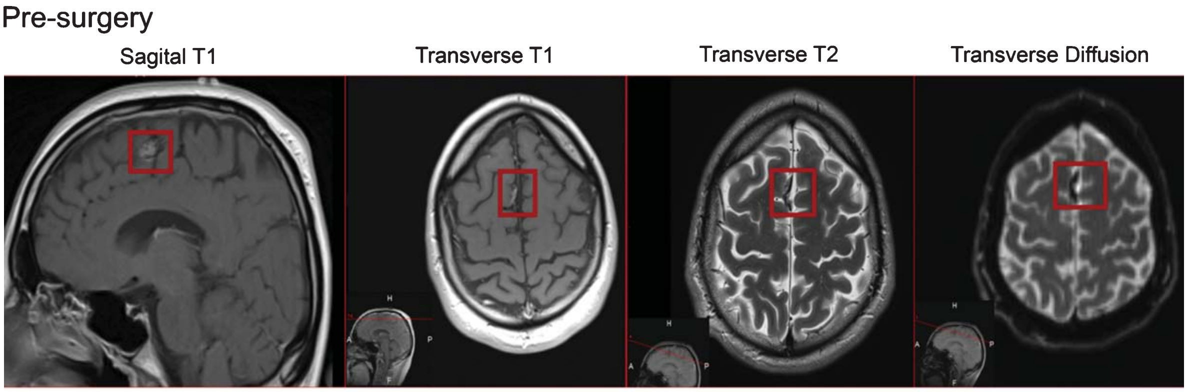

Fig. 1. Case 1 Patient's MRI demonstrates a calcification of the right falx located at the dorsal ACC extending into the supplementary motor area before and after resection.

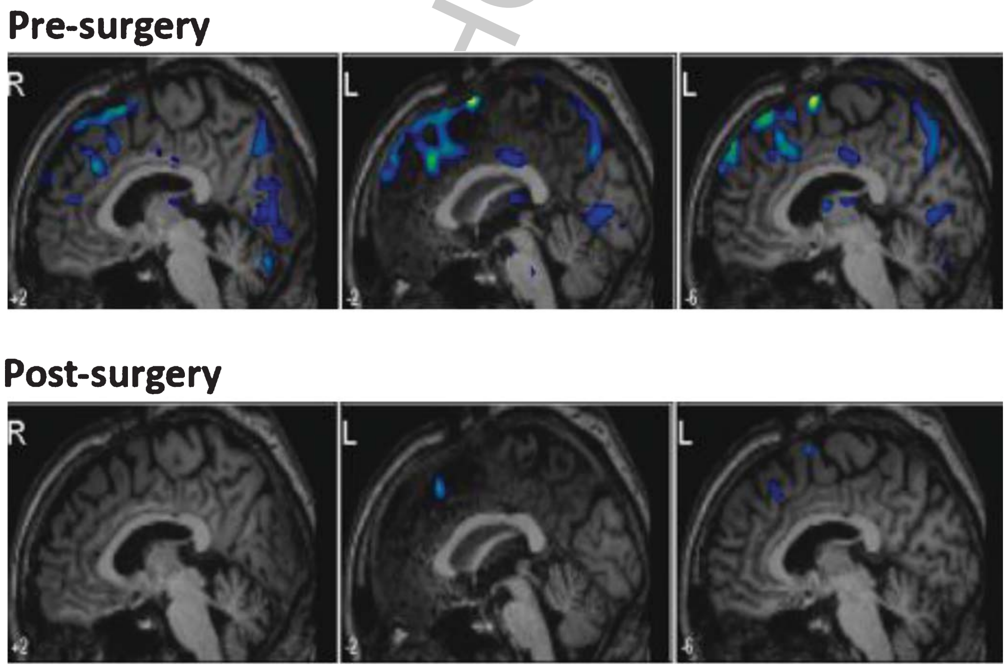

Fig. 2. Case 1 Patient's fMRI demonstrates a BOLD signal at the dorsal anterior cingulate cortex evoked by tinnitus-matched frequency presentation in the scanner pre- surgery but not post-surgery.

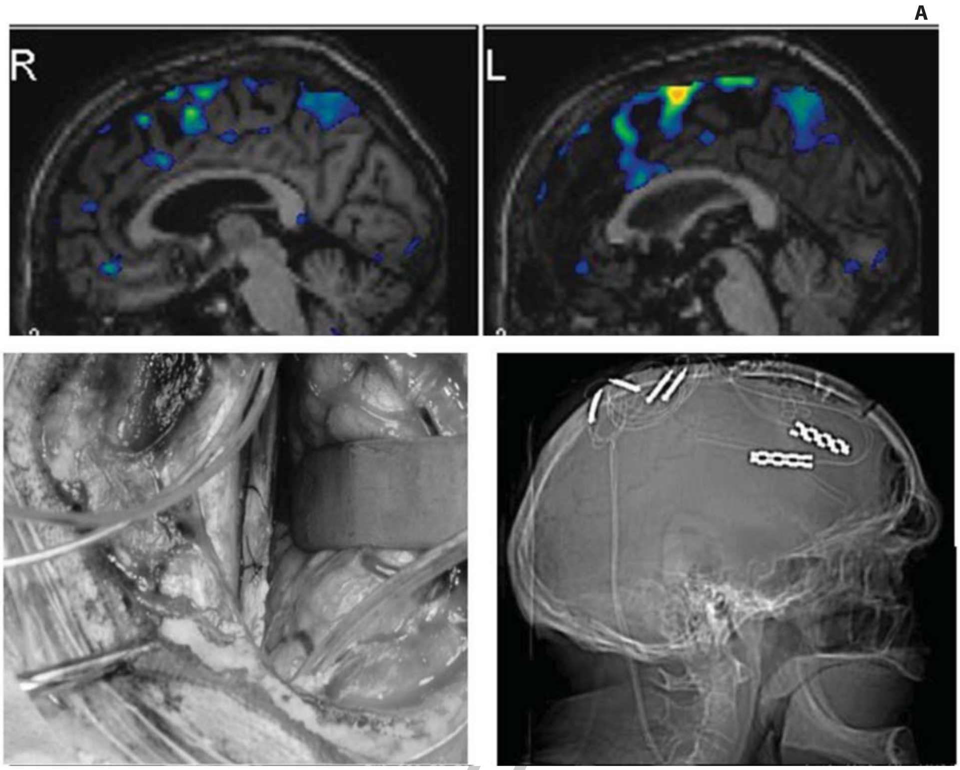

Fig. 3. Case 2 Top: Patient's fMRI demonstrates a BOLD signal at the dorsal anterior cingulate cortex evoked by tinnitus matched frequency presentation in the scanner; Below: patient implanted with a bilateral electrode targeting the dorsal ACC.

The tinnitus matching demonstrated that the tinnitus was centered at 4000 Hz, 10 dB above the hearing threshold, and was associated with high-pitch hearing loss. Treatment with flupentixol + melitracen (Deanxit) and clonazepam (Meeus, De Ridder, & Van de Heyning, 2011) did not benefit the patient, nor did cyclobenzaprine (Vanneste, Figueiredo, & De Ridder, 2012), naltrexone (Vanneste, Azevedo, & De Ridder, 2013), or acamprosate (Azevedo & Figueiredo, 2005). A small improvement on the right side was reported by wearing a hearing aid and noise masker to a NRS score of 8/10 for loudness and 10/10 for distress. Non-invasive neuromodulation trials were proposed.

The CT brain was unremarkable and MRI showed multiple white matter lesions which might or might not be related to the symptoms of the patient (Nowe, Van de Heyning, & Parizel, 2007). A resting state source-localized (sLORETA) EEG was performed to visualize abnormal brain activity, which can be used to determine targets for non-invasive neuromodulation. A small improvement on the right side was noted by wearing a combination hearing aid with noise masker to 8/10 for loudness and 10/10 for distress on NRS.

Since the patient was intractable, neuromodulation trials were proposed, consisting of transcranial magnetic stimulation (TMS) of the auditory cortex (De Ridder et al., 2005), bifrontal transcranial direct current stimulation (tDCS) (Vanneste & De Ridder, 2011), and transcutaneous electrical nerve stimulation (TENS) of the C2 nerve (Vanneste, Plazier, Van de Heyning, & De Ridder, 2010). None of these three techniques yielded any benefits to the patient.

Therefore, an fMRI was requested according to a protocol previously described (De Ridder et al., 2004; Smits et al., 2007), but was adjusted to the patients individual tinnitus matched frequency (De Ridder, Vanneste, Kovacs, Sunaert, Menovsky, et al., 2011). The pathological BOLD activation could be used as a target for neuromodulation using a neuronavigated system (De Ridder et al., 2004; 2012). Pathological activity was considered to be BOLD activation elicited by 4000 Hz sound presentation (his tinnitus frequency) but not by a control frequency (1000 Hz) (see Fig. 3).

After obtaining ethical approval from the ethical committee at the University Hospital in Antwerp, Belgium and informed consent from the patient, an open neurosurgical approach was performed consisting of a small right-sided frontal craniotomy for a transfalcine approach inserting two electrodes for bilateral dACC stimulation, as previously described (De Ridder, Joos, et al., 2016; De Ridder et al., 2017; De Ridder, Manning, et al., 2016).

In short, after induction of anesthesia, intubation, and ventilation, the patient was fixed in the Mayfield head rest in supine position, his neck slighted flexed with zero degrees rotation. After registration of the preoperatively administered skin fiducials for neuronavigation with the Stealth® frameless stereotactic system, the patient's head was disinfected and draped in a sterile fashion. A laterolateral frontal incision was made within the hairline crossing the midline, followed by a 4 cm × 4 cm right frontal craniotomy crossing the superior sagittal sinus. Subsequently, the dura was incised in U-shape fashion and reflected across the midline. This was followed by a neuronavigated approach between the right frontal lobe and the falx. Once the target was localized, the falx was incised and 2 lamitrode 44 (SJMedical, neurodivision, Plano, Tx, USA) electrodes were sutured back to back and inserted with the fMRI BOLD activity as the target (Fig. 3). The electrodes were sutured to the falx, the operative site was thoroughly rinsed, the dura was closed in a primary fashion, and the bone was repositioned and fixed. The skin was then closed and the patient was relieved from the headrest and woken up from anesthesia.

On the first postoperative day, the electrodes were activated in 6 Hz tonic mode. The electrode pole configuration was +-+-+-+- in order to generate a large stimulation field. On the second postoperative day the patient was discharged. Six Hz was selected as a similar frequency because 5 Hz yielded the best result with TMS.

After one week, the subject was evaluated and his clinical state had dramatically improved. All measures were close to halved in severity. The subject's distress was reduced from 9/10 to 5/10 as measured by the NRS, or from grade 4 (very severe tinnitus, psychologically decompensated) to grade 2 tinnitus (moderate). His subjective loudness perception decreased from 10/10 to 5/10 in the right ear and from 8/10 to 4/10 in the left ear. Additionally, the percentage of time that the tinnitus was dominantly present halved from 100% to 50%. After 4 weeks, his stimulation design was altered to verify if further improvement could be obtained. A recently developed novel stimulation design was used consisting of 6 Hz burst mode, containing 5 spikes at 500 Hz spike mode, with 1000 μsec pulse width at 1.4 mA. (De Ridder, Vanneste, Plazier, van der Loo, & Menovsky, 2010; De Ridder, Vanneste, van der Loo, et al., 2010) in an attempt to improve his clinical outcome. Burst stimulation was provided by an Eon IPG (SJMedical, Neurodivision, Plano, Texas, USA) programmed with a custom-made device. Indeed, the subject's distress was further reduced to 3/10, remaining in the moderate range, and his subjectively perceived loudness was further reduced on the left (his worst ear) to 3/10 and remained at 4/10 on the right. His anxiety and depression scores improved from 13 to 6 and from 13 to 8 respectively.

Other burst frequencies were also tested: 2, 4, 8 and 10 Hz, but 6 Hz burst mode remained clinically superior and was therefore maintained. His beneficial effect has remained for 2 years.

2.2. *Cognitive and emotional counting Stroop task*

The Stroop task is one of the most studied cognitive paradigms in investigating the ACC (Gasquoine, 2013; Mansouri, Tanaka, & Buckley, 2009). This task measures the ability to focus selectively on one dimension of a stimulus while ignoring an irrelevant one (Hayward et al., 2004). In a typical Stroop task, the subject is presented with a stimulus with two dimensions (e.g. a color-word written in a specific font-color) and required to respond to one of the two aspects of the stimulus (e.g. name the color of the font) and ignore the other (e.g. ignore the word) (Sahinoglu & Dogan, 2016). In this study, a cognitive and emotional counting Stroop task was used to explore the cognitive and emotional processing of the two patients before and after the intervention. In Case 1 both tasks were collected 2 days before surgery, five days after surgery, and at a 3 month follow-up. For Case 2, both tasks were assessed after implantation on 3 different time points with one week between each session, beginning from one month after implantation. Data were collected without stimulation (off) and with stimulation (on). There were 2 sessions of on stimulation, one with the patient aware that the stimulation was on and one with the patient unaware the stimulation was on. Immediately after implantation the stimulator was set active (on) for three weeks. Three weeks after implantation, the participant returned to change the stimulation parameter from active (on) to inactive (off). One week after the stimulator was set from on to off, the participant was invited to perform the cognitive and emotional counting Stroop task for the first time ("off"). After the participant had performed the cognitive and emotional counting Stroop task the stimulator was set from inactive (off) to active (on). The participant returned seven day later to perform the cognitive and emotional counting Stroop task for the second time with stimulation on ("on known"). After the participant had performed the cognitive and emotional counting Stroop task with the stimulation on, the experimenter stated to change the stimulation parameters again, however the stimulator remained on active (on unknown). The participant returned seven day later to perform the cognitive and emotional counting Stroop task for the third time with the stimulation on ("on unknown").

2.2.1. Cognitive counting Stroop task

The cognitive Stroop task is a standardized test that measures attention based on reaction time using congruent and incongruent situations. Specifically, the cognitive Stroop Task evaluates the top-down executive function portion of the attention network specific to selective attention (MacLeod, 1991). Results from this task represent a measurement of one's attention capabilities needed to overcome "interference" as mandated by the classical Stroop Task. The Stroop effect is described as the interference that occurs between the instinctive process of identifying the meaning of a word and the ability to identify the physical number (or color) of words presented. The number of words (or color) can differ from the meaning (incongruence) or be the same as the meaning (congruence). Interference is demonstrated by the difference in reaction times between the congruent and incongruent trials (MacLeod, 1991). In our cognitive counting Stroop task, the participant is asked to focus on a "+" in the middle of a blank white screen. Then a number word (e.g. "one") appears on the screen 1–4 times for 1.4 seconds. The objective of the task is to select how many times the word appeared using a keyboard. So, if the word "one" appeared 3 times on the screen, the subject should select 3 on the keyboard. This represents an incongruent trial. If the word "one" had only appeared one time on the screen, it would be a congruent trial. Stimuli included the words "one", "two", "three", and "four". There were a total of 48 congruent trials and 48 incongruent trials that were presented in a completely randomized order.

2.2.2. Emotional counting Stroop task

The emotional counting Stroop Task is similar to the cognitive counting Stroop task, it only differs in the stimuli used: emotional words (e.g. "danger") or neutral words (e.g. "curtain" or "table"). Specifically, the emotional counting Stroop task is known to evaluate the top-down executive control portion of the attention network (specific to selective attention) with the added interaction of anxiety (Andersson, 2002; Andersson, Eriksson, Lundh, & Lyttkens, 2000). Therefore, we can utilize the outcomes of this task and the cognitive Stroop to determine whether Stroop results are related more to selective attention capabilities or are a result of increased anxiety and emotion (Ashley, Honzel, Larsen, Justus, & Swick, 2013). The task procedure is similar to the cognitive counting Stroop task, such that the participant must select on a keyboard the number of times a word appears on the screen. There is still a focusing object "+" to recenter the participant's field of vision after each trial. Timing characteristics were the same as the cognitive counting Stroop Task. Emotional stimuli included the words "violence", "deceit", "murder", "contempt", "painful", "hazard", "torture", and "danger". Neutral stimuli included the words "table", "cushion", "curtain", "pan", "mirror", "bowl", "cabinet", and "closet". Stimuli were chosen based on a previous study (Whalen et al., 1998). There were a total of 48 emotional trials and 48 emotionally neutral trials that were randomized with a 1.4 second word presentation duration.

3. Results

3.1. Case 1

A comparison between different conditions for both the emotional and cognitive Stroop tasks between the 3 different time points (pre- surgery, post-surgery, 3 months follow-up) did not show any significant different for the amount of errors made (Table 1).

A mixed model with cognitive Stroop (congruent vs. incongruent) and condition (pre-surgery, post-surgery and 3 months follow-up) as fixed variables and reaction time (RT) as dependent variable revealed a main effect for cognitive Stroop ($F = 7.92$, $p = 0.008$), demonstrating that the participant was faster for congruent trials ($M = 579.69$ ms, $Sd = 107.41$ ms) than incongruent

Table 1
Number of errors made in the cognitive and emotional counting Stroop tasks

	Task	Conditions	Pre-surgery	Post-Surgery	3 months follow-up
Case 1	Cognitive	Congruent	2	1	1
		Incongruent	1	0	1
	Emotional	Emotional	0	1	1
		Neutral	1	1	2
			Off	On (Unknown)	On (Known)
Case 2	Cognitive	Congruent	0	1	0
		Incongruent	2	1	2
	Emotional	Emotional	1	2	1
		Neutral	1	1	2

trials ($M = 633.87$ ms, $Sd = 83.33$ ms). Also, a main effect for condition ($F = 12.92$, $p < 0.001$) was obtained, indicating a significant difference between the 3 months follow-up ($M = 558.26$ ms, $Sd = 72.45$ ms) and respectively pre-surgery ($M = 674.58$ ms, $Sd = 102.11$ ms; $p < 0.001$) and post-surgery ($M = 632.01$ ms, $Sd = 69.66$ ms; $p = 0.027$). No significant effect was obtained between pre-surgery and post-surgery ($p = 0.09$). In addition, a significant interaction effect between cognitive Stroop × condition ($F = 3.17$, $p = 0.05$) was found. No significant effect was obtained between congruent and incongruent trials pre-surgery ($t = 0.27$, $p = 0.80$). For post-surgery ($t = 2.98$, $p = 0.011$) as well as the 3 month follow-up ($t = 4.32$, $p = 0.001$), a significant effect was obtained showing faster RTs for congruent trials than incongruent trials. See Fig. 4A for overview.

For the emotional counting Stroop task, a mixed model with emotional counting Stroop (emotional vs. neutral) and condition (pre-surgery, post-surgery and 3 months follow-up) as fixed variables and reaction time (RT) as dependent variable also revealed a significant main effect for emotional Stroop ($F = 4.63$, $p = 0.033$), indicating that the participant was faster for neutral trials ($M = 562.69$ ms, $Sd = 114.32$ ms) than emotional trials ($M = 604.12$ ms, $Sd = 173.58$ ms). In addition, a main effect for condition ($F = 9.84$, $p < 0.001$) was demonstrated, indicating a significant difference between 3 months follow-up ($M = 525.74$ ms, $Sd = 99.41$ ms) and respectively pre-surgery ($M = 625.84$ ms, $Sd = 177.03$ ms; $p < 0.001$) and post-surgery ($M = 585.4$ ms, $Sd = 120.09$ ms; $p = 0.032$). No significant effect was obtained between pre-surgery and post-surgery ($p = 0.20$). No significant interaction effect was obtained between emotional Stroop × condition ($F = 0.003$, $p = 0.99$). See Fig. 4B for overview.

3.2. Case 2

A comparison between different conditions for both the emotional and cognitive Stroop tasks between the three different time points (off, on unknown, on known) did not show any significant difference for the amount of errors made (Table 1).

A mixed model with cognitive Stroop (congruent vs. incongruent) and condition (off, on (unknown), and on (known)) as fixed variables and reaction time (RT) as dependent variable showed a main effect for cognitive Stroop ($F = 4.12$, $p = 0.047$), demonstrating that the participant was faster for congruent trials ($M = 727.32$ ms, $Sd = 159.98$ ms) than incongruent trials ($M = 792.84$ ms, $Sd = 124.42$ ms). Also, a main effect for condition ($F = 18.76$, $p < 0.001$) was obtained, indicating a significant difference between off ($M = 897.72$ ms, $Sd = 124.81$ ms) and both on (unknown) ($M = 741.67$ ms, $Sd = 122.55$ ms; $p < 0.001$) and on (known) ($M = 690.22$ ms, $Sd = 94.17$ ms; $p < 0.001$). No significant effect was obtained between on (unknown) and on (known) ($p = 0.83$). In addition, a significant interaction effect between cognitive Stroop × condition ($F = 3.54$, $p = 0.043$) was detected. No significant effect was obtained between congruent and incongruent trials in the off condition ($t = 0.75$, $p = 0.47$). For both on (unknown) ($t = 2.03$, $p = 0.06$) and on (known) ($t = 2.89$, $p = 0.011$), a significant effect was obtained showing faster RTs for congruent trials than incongruent trials. See Fig. 4C for overview.

For the emotional counting Stroop task, a mixed model with emotional counting Stroop (emotional vs. neutral) and condition (off, on (unkown), and on (known)) as fixed variables and reaction time (RT) as dependent variable revealed no significant main effect for emotional Stroop ($F = 0.45$, $p = 0.50$). A main effect for condition ($F = 4.15$, $p = 0.017$) was demonstrated, indicating a significant difference

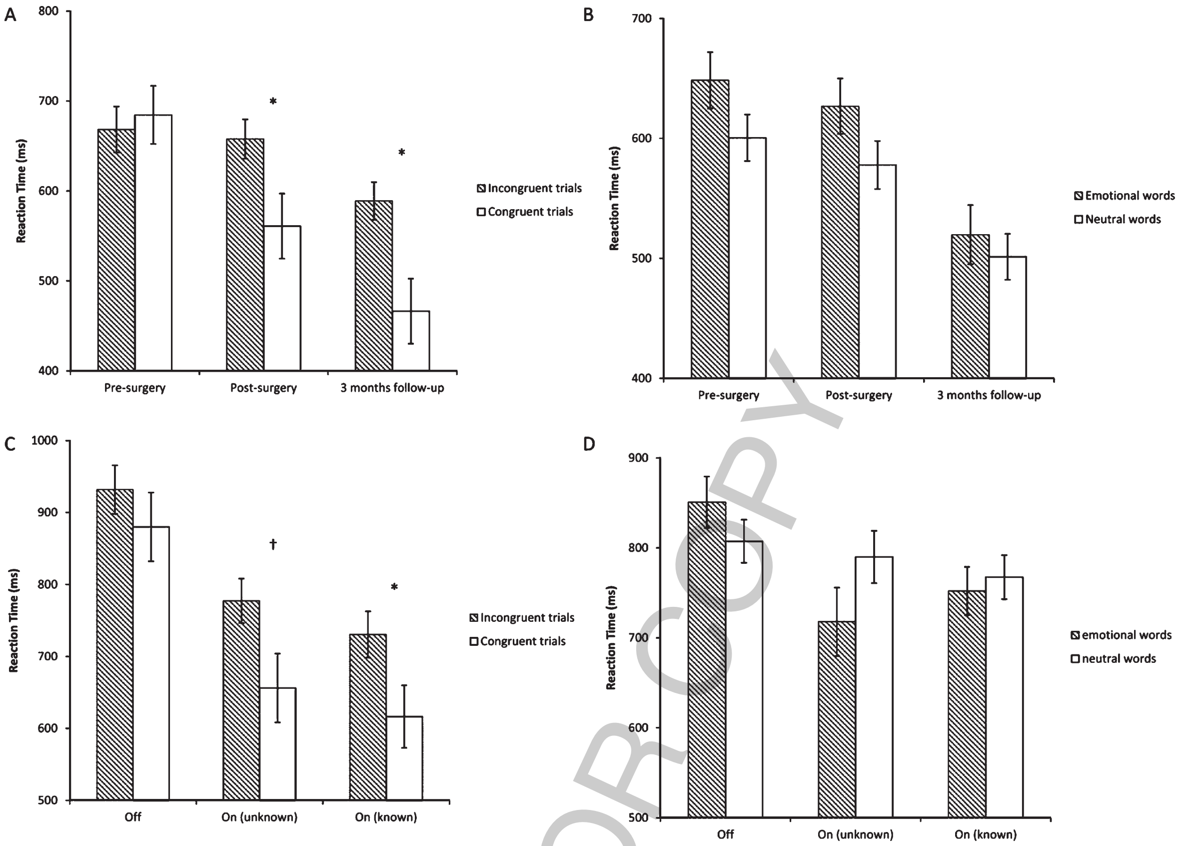

Fig. 4. The reaction times on the cognitive and emotional counting Stroop tasks for Case 1 and Case 2. (A) Case 1 Cognitive Stroop: significant interaction effect between cognitive Stroop and condition. No significant effect was obtained between congruent and incongruent trials pre-surgery. For post-surgery as well as the 3 month follow-up, a significant effect was obtained showing faster RTs for congruent trials than incongruent trials. (B) Case 1 Emotional Stroop: no significant interaction effect between emotional Stroop and condition. (C) Case 2 Cognitive Stroop: significant interaction effect between cognitive Stroop and condition. No significant effect was obtained between congruent and incongruent trials in the off condition. For both on (unknown) and on (known) a significant effect was obtained showing faster RTs for congruent trials than incongruent trials. (D) Case 2 Emotional Stroop: no significant interaction effect was obtained between emotional Stroop and condition.

between off ($M = 835.06$ ms, $Sd = 151.82$ ms) and both on (unknown) ($M = 760.30$ ms, $Sd = 147.98$ ms; $p = 0.041$) and on (known) ($M = 761.12$ ms, $Sd = 155.62$; ms; $p = 0.044$). No significant effect was obtained between the on (unknown) and on (known) conditions ($p = 0.99$). No significant interaction effect was obtained between emotional Stroop × condition ($F = 2.17$, $p = 0.12$). See Fig. 4D for overview.

4. Discussion

In this study, we aimed to provide a better understanding of the role of the dACC using a cognitive and emotional counting Stroop task in two extraordinary cases. We analyzed the findings of two cases that had abnormalities at the dACC and were treated in different ways (calcification excision and anterior cingulate implant). We hypothesized that the dACC intervention in both patients would result in improved performance in the cognitive and emotional parts of the adjusted counting Stroop task, supporting a more general role of the dACC. The results of these cases contribute to previous knowledge, which is mostly based on neuroimaging studies, as it is able to provide causal implications for the role of the dACC in patients.

In both patients, we found an overall improvement on the emotional, the cognitive, and the neutral trials of the counting Stroop task after the interventions. These findings support the idea of the dACC being involved in more general processing functions, rather than only cognitive processing. Although the dACC has been demonstrated to be involved in the cognitive counting Stroop (Bush et al., 2000; 1998), the study of Davis and colleagues provided electrophysiological data at the single-cell level for involvement of the dACC in attention demanding tasks (i.e. Stroop), including those with an emotional overlay as measured by the emotional counting Stroop task (Davis et al., 2005). The study reported that the dACC contains neurons that respond differentially to emotional trials but not to incongruent cognitive trials, countering the simple subdivisions of the ACC of the caudal/dorsal cognitive division and the rostral/ventral affective division. The researchers argue that dACC neurons may be acting as salience detectors when faced with conflict and difficult emotional stimuli. Salient is a term used to describe a stimulus or an aspect of a stimulus that stands out, which can be influenced by previous experiences, memories, current psychological state, goals, and drives (Goldberg, Bisley, Powell, & Gottlieb, 2006; Puglisi-Allegra & Ventura, 2012; Uddin, 2015). The finding that neither patient in this study showed a cognitive Stroop effect before surgery or when not receiving stimulation, yet both showed a cognitive Stroop effect after surgery and during stimulation of the dorsal anterior cingulate cortex is in line with the concept of the dACC as a salience detector. It is known that the dACC becomes more involved when a task becomes more demanding (Davis et al., 2005). When modulating the dACC, neuronal response to high conflict words (incongruent words, including those with emotional valence) may recruit more neuronal activity within the dACC to accomplish a given task.

Our findings are in line with the idea of salience processing through a "salience network" which includes key nodes in the insular cortices as well as the dACC (Uddin, 2015). The salience network is suggested to have a central role in the detection of behaviorally relevant stimuli (i.e. stimuli that are important to an individual) and the coordination of neural resources (Uddin, 2015), and it comprises one of the many theories trying to explain the (dorsal) ACC's function. Interestingly, the salience network is also suggested to mediate switching between activation of the default-mode network (DMN) and the central executive network (CEN) to guide appropriate responses to salient stimuli (Uddin, 2015). Thus, modifying a 'causal hub' of the salience network can influence key nodes of other large-scale brain networks, including the CEN and DMN (Uddin, 2015). The dACC has also been suggested as a promising target for therapeutic brain stimulation because this region, along with the anterior insula (i.e. the salience network), has been found to be one of the core brain regions affected across most psychiatric disorders (De Ridder, Vanneste, et al., 2016; Downar et al., 2016). It still needs to be explored whether treatments that restore the functioning of the salience network can have particular broad spectrum benefits across psychiatric disorders, particularly comorbid cases, by enhancing the general capacity for self-driven cognitive control and response inhibition (Downar et al., 2016).

In this study, both tinnitus patients experienced tinnitus improvements as well as general improvement on the cognitive and emotional counting Stroop tasks, pointing to a general improvement on all trial types. However, it is unclear whether the dACC treatment improved the tinnitus and in turn influenced the subjects' general cognitive and emotional processing as reflected by improved performance on the cognitive and emotional counting Stroop tasks. Contrarily, the treatment may have improved cognitive and emotional processing which subsequently influenced the subjects' tinnitus. In pain research targeting the dACC, researchers found no improvement at a group level on the intensity of pain; however, an improvement was noted in quality of life (Boccard, Fitzgerald, et al., 2014; Boccard, Pereira, et al., 2014). They suggested that the improvement was mediated via the affective or attentional component of the pain.

Looking into the cognitive component of the experiment, the cases did not reflect a Stroop or interference effect (i.e. a significant slower reaction time for the incongruent trials compared to the congruent trials) at the baseline measures, as the reaction times on the incongruent trials are similar to the reaction times on the congruent trials. This might be the result of general tardiness due to abnormality in the dACC, due to either the lesion or another tinnitus-related functional irregularity (Vanneste, Faber, Langguth, & De Ridder, 2016). After the interventions, a substantial drop in reaction time was reported in both types of trials, but more notably in the congruent trials, reflecting a Stroop effect. The presence of the Stroop effect after the intervention can be interpreted as a normalization of the interference effect.

These two unique cases have provided insight into the role of the dACC in cognitive and emotional processing. However, we must acknowledge some limitations to our study. Our findings are based on two cases and the findings should therefore be interpreted with caution. Nevertheless these cases are both exceptional. Furthermore, it was not possible to elucidate the exact neural mechanisms at play in this study since we did not use any neuroimaging techniques during the experiment due to the limitations of imaging after implantation.

5. Conclusion

These two cases add to our understanding of the role of the dACC by using a cognitive and emotional counting Stroop task, and they provide direct causal evidence from two different approaches. The results reveal that the dACC is not just a subregion of the ACC that contributes to one specific cognitive function. Rather it is part of the salience network and contributes to general brain functioning, influencing both cognitive and emotional processing. Future research should further investigate the role of the dACC in influencing important brain networks and as a potential treatment target for clinical intervention.

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