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Functional brain networks associated with the urge for action: Implications for pathological urge

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ABSTRACT

Tics in Tourette syndrome (TS) are often preceded by sensory urges that drive the motor and vocal symptoms. Many everyday physiological behaviors are associated with sensory phenomena experienced as an urge for action, which may provide insight into the neural correlates of this pathological urge to tic that remains elusive. This study aimed to identify a brain network common to distinct physiological behaviors in healthy individuals, and in turn, examine whether this network converges with a network we previously localized in TS, using novel 'coordinate network mapping' methods. Systematic searches were conducted to identify functional neuroimaging studies reporting correlates of the urge to micturate, swallow, blink, or cough. Using activation likelihood estimation meta-analysis, we identified an 'urge network' common to these physiological behaviors, involving the bilateral insula/claustrum/inferior frontal gyrus/supplementary motor area, mid-/anterior- cingulate cortex (ACC), right postcentral gyrus, and left thalamus/precentral gyrus. Similarity between the urge and TS networks was identified in the bilateral insula, ACC, and left thalamus/claustrum. The potential role of the insula/ACC as nodes in the network for bodily representations of the urge to tic are discussed.

1. Introduction

There are many everyday physiological processes that while primarily reflexive, can also be controlled voluntarily e.g., the suppression of normal blinking (Berman et al., 2012; Mazzone et al., 2011; Zald and Pardo, 1999). However, while these natural behaviors can be voluntarily inhibited by the individual, this is associated with a buildup of an urge that cannot be controlled indefinitely (Berman et al., 2012). This '*urge for action*' is suggested to drive the individual to perform various behaviors including micturition, swallowing, and yawning (Berman et al., 2012; Jackson et al., 2011; Stern et al., 2020). Over the past two decades, neuroimaging investigations have begun to uncover the neural mechanisms of the urge for action in healthy individuals (Berman et al., 2012; Blok, 1997; Jackson et al., 2011; Mazzone et al., 2007). Indeed, using task-based functional magnetic resonance imaging (fMRI), several brain regions associated with interoception, somatosensory processing, and movement preparation (Critchley et al., 2004; Lee et al., 1999; Schulz, 2016) have been implicated in natural physiological urge in healthy individuals, namely the insula and regions of the sensorimotor cortex, including the mid-cingulate gyrus, pre- and post-central gyri, and supplementary motor area (SMA) (Berman et al., 2012; Jackson et al., 2011; Lerner et al., 2009; Mazzone et al., 2011; Stern et al., 2020).

Previous research has drawn parallels between natural physiological urge for action and aspects of pathology in neurodevelopmental and neuropsychiatric disorders such as Tourette syndrome (TS), autism spectrum disorder, and obsessive-compulsive disorder (OCD) (Jackson et al., 2011; Stern et al., 2020). Specifically, many primary symptoms within these disorders are thought to be associated with sensory phenomena in addition to cognitions (e.g., "just right" phenomena) that urge the individual to perform an action or compulsion (Cavanna et al., 2017; Jackson et al., 2011; Singh et al., 2019; Stern et al., 2020). For example, while tics remain the behavioral hallmark of TS (Robertson et al., 2017), it is well recognized that these are often preceded by uncomfortable internal sensations, termed 'premonitory urges' (Efron and

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Dale, 2018; Houghton et al., 2014; Leckman et al., 2006). Although not a diagnostic criterion of TS, premonitory urges are common and reported in >90 % of patients, particularly older adolescents and adults (Cavanna et al., 2017; Leckman, 1993; Reese et al., 2014; Woods et al., 2005). Similar to many natural physiological behaviors, while tics can be voluntarily suppressed by the individual, as tic suppression continues, the urge to tic often increases in intensity and becomes more difficult to control (Cohen et al., 2013; Jackson et al., 2021). Early reports of premonitory urge in relation to tics describe these sensory phenomena to be the original "cause" of these behaviors, that these sensory phenomena perpetuate tics, and that suppression of tics results in discomfort (Patrick, 1905; Meige and Feindel, 1907). Importantly, many individuals with TS believe that their tics are partial or fully voluntary responses to these internal aversive sensations to temporarily alleviate them (Bliss et al., 1980; Kwak et al., 2003; Lang, 1991; Reese et al., 2014). Accordingly, it has been suggested that tics may be conditioned responses to premonitory urges (Fründt et al., 2017) and, therefore, interfering with this '*urge-tic-relief*' cycle is currently central to behavioral interventions for TS (Woods et al., 2008). However, the neural mechanisms of these sensory urge phenomena are not yet fully understood.

Recently, using a novel neuroimaging method called 'coordinate network mapping' (CNM), we localized a brain network for TS based on whole-brain structural alterations relative to healthy controls (Zouki et al., 2023). CNM is a network mapping method that leverages a large normative dataset of fMRI scans ($n = 1000$) (Holmes et al., 2015; Yeo et al., 2011) used to identify the set of brain regions (i.e., network) that show common functional connectivity between disparate structural differences from existing clinical neuroimaging findings (Darby et al., 2019). When applying CNM to previously published coordinates of structural alterations in TS, we identified a network defined by positive functional connectivity to the basal ganglia, insula, anterior cingulate cortex (ACC), thalamus, and cerebellum, and negative connectivity to the occipital lobe and precuneus. Using a similar technique termed lesion network mapping, we also demonstrated that these brain regions are largely consistent with a network derived from lesions causing tics (Zouki et al., 2023). Of note, several of the brain structures within this '*TS network*' also appear to be implicated in natural physiological urge for action.

In an earlier seminal study employing ALE meta-analysis, Jackson et al. (2011) demonstrated that the urge to micturate and swallow, and task-related fMRI correlates of the urge to yawn in healthy individuals, commonly activated the anterior insula and mid-cingulate cortex. Using previously published fMRI correlates of tic expression (Bohlhalter, 2006), the authors showed that these structures are also active before tic onset, which may reflect the neural activity associated with the urge to tic in TS (Jackson et al., 2011). These findings demonstrated that common neural mechanisms may underlie both natural urge for action in healthy individuals and pathological urges in TS. In recent years, a growing body of research has examined the functional neural correlates of natural physiological urges across various behaviors in healthy individuals, including those phenomenologically similar to simple motor and vocal tics, such as blinking and coughing (Jankovic, 2001). However, to our knowledge, no study has yet investigated whether the urges associated with these anatomically distinct physiological behaviors (micturition, swallowing, blinking, coughing) activate common brain regions. Further, by examining commonalities between brain regions activated by these physiological urges and our previously localized TS network, the mechanisms of this network in the urge to tic might be better understood. In other words, uncovering the neural mechanisms of physiological urge in healthy individuals may help elucidate the neurobiology of the phenomenologically similar premonitory urge to tic in TS, which could contribute to the development of more targeted behavioral therapy to interfere with the urge-tic-relief cycle.

The aim of this study was to first use ALE meta-analysis to identify whether a common set of brain structures are activated across the urge to micturate, swallow, blink, and cough in healthy individuals. We then examined the similarity between this 'urge network' in healthy individuals and the TS network derived from patients with primary tics, previously localized using CNM (Zouki et al., 2023), in order to identify regions that may be associated with the premonitory urge to tic in TS patients.

2. Materials and methods

2.1. Study selection

2.1.1. Systematic search

MEDLINE Complete and Embase databases were searched in April 2022 for functional neuroimaging studies reporting the brain activation correlates of physiological urges associated with micturition, swallowing, blinking, or coughing in healthy individuals. Separate systematic searches were conducted for each behavioral domain using a combination of synonyms specific to each behavior; magnetic resonance imaging (MRI); fMRI; single photon emission computed tomography (SPECT); and positron emission tomography (PET) (see Supplementary material for full search syntax for each behavioral domain). Searches were updated in December 2023 using the same syntax, limiting the search to studies published between March 2022 and December 2023. These neuroimaging methods were chosen based on their ability to demonstrate task-related changes in blood flow and metabolism in the brain. No publication or year limiters were applied, however, only studies available in English were considered. The reference lists of included articles were assessed for possible studies missed in the initial search.

2.1.2. Inclusion and exclusion criteria

Studies were selected for the ALE meta-analyses based upon the following inclusion criteria: (i) published studies using a block or event-related design to identify the brain activation correlates associated with the urge to micturate, swallow, blink, or cough in healthy individuals >18 years old; (ii) having a contrast to a rest period or alternative suitable control condition; (iii) utilizing whole-brain analysis [i.e., not restricting the analysis to regions of interest (ROI)] (Eickhoff et al., 2009); and (iv) reporting activation coordinates in standard stereotaxic space (x, y, z) [Talairach or Montreal Neurological Institute (MNI)]. Neuroimaging experiments comparing brain activity between patient populations and healthy controls were only included in the current analyses if the authors reported activation coordinates separately for the control group (see Supplementary material for inclusion and exclusion criteria specific to each behavioral domain).

2.1.3. Screening and data extraction

After the removal of duplicates, the initial 50 titles and abstracts of each search were reviewed by two reviewers to ensure inter-researcher agreement. The remaining titles and abstracts were screened by one reviewer using EndNote (version X9) and Rayyan software (Ouzzani et al., 2016) before assessing full-text articles in EndNote. Disagreements were resolved through discussion to reach a consensus, and where necessary, with input from a senior author. Following full-text screening, we extracted the demographic characteristics of each study sample, neuroimaging modality used, main task design and paradigm, control task, and stereotaxic coordinates associated with the main contrast of interest. Coordinates were included in each analysis at corrected and/or uncorrected thresholds (for example, uncorrected $p < 0.001$). Coordinates reported as 'trends' by the authors were excluded to identify consistent activations within each behavioral domain without reducing the specificity of the analyses.

2.2. Activation likelihood estimation meta-analyses

We conducted four separate ALE meta-analyses using GingerALE (version 3.0.2) to test for regions of consistent significant activation associated with the urge to micturate, swallow, blink, or cough. We chose to implement ALE meta-analysis rather than CNM in this context as these coordinates were derived from task-based functional neuroimaging paradigms, rather than neuroimaging methods measuring brain structure or metabolic changes at rest (Darby et al., 2019). Functional neuroimaging methods investigating task-related brain activity are associated with a higher signal-to-noise ratio and greater anatomical specificity given the presence of greater activation with task onset. As such, task-related functional neuroimaging findings generally involve less dispersion of the involved brain regions when a homogenous task is used. Therefore, conducting separate ALE meta-analyses for each behavioral domain was the most appropriate method for testing our hypothesis.

Before all analyses, coordinates reported in Talairach space were transformed to MNI space using the Yale BioImage Suite converter (Lacadie et al., 2008). We used the revised ALE algorithm (Eickhoff et al., 2012), which applies a random-effects model (Eickhoff et al., 2009), with refined permutation testing and stringent correction for multiple comparisons (Eickhoff et al., 2012). The significance of the ALE maps was assessed using a cluster-forming threshold of $p < 0.001$ (uncorrected), 1000 permutations, and corrected for multiple comparisons using a cluster-level interference threshold of FWE $p < 0.05$. For the analyses of the urge to micturate and blink, minimal clusters of consistent activation were identified at this threshold i.e., ≤ 2. To allow for the identification of consistent activation across the four physiological urges, exploratory analyses for these behaviors were performed following previously reported methods (Ellis et al., 2023; Zouki et al., 2023), using a threshold of $p < 0.001$ (uncorrected) with a cluster extent of 100 mm^3.

2.3. Localizing a network for natural physiological urge

To examine which brain regions are consistently activated by the urge to micturate, swallow, blink, and cough, the similarity between the four brain networks derived from the aforementioned ALE meta-analyses was assessed using FSLeyes software (version 0.34.2) (Jenkinson et al., 2012). Regions common to ≥ 2 behaviors were defined as voxels falling within our urge network. The neuroanatomical location of the regions of network similarity was confirmed using the Harvard-Oxford cortical and subcortical structural atlases (FSL; version 6.0.4) (Jenkinson et al., 2012).

2.4. Network similarity between the urge for action and Tourette syndrome

We previously localized a functional network implicated in TS (Zouki et al., 2023), using a novel network mapping technique termed CNM (Darby et al., 2019). Briefly, using previously published coordinates of structural alterations in TS patients relative to healthy controls, CNM was used to leverage a large normative dataset of fMRI scans ($n = 1000$) (Holmes et al., 2015; Yeo et al., 2011) to localize the set of brain regions which are functionally connected to these disparate neuroimaging findings (Darby et al., 2019). This identified a network defined by positive functional connectivity to the basal ganglia, insula, ACC, thalamus, and cerebellum, and negative connectivity to the occipital lobe and precuneus (Zouki et al., 2023). In the present study, we examined the anatomical similarity between this previously localized TS network and the identified urge network by overlapping these using FSLeyes software (version 0.34.2) (Jenkinson et al., 2012). It should be noted that the lesion-induced tic network we also localized in our previous study (Zouki et al., 2023), using lesion network mapping, was not of interest in the present study, as here we were interested in neuroimaging findings in patients diagnosed with TS, rather than lesion-induced tics.

2.5. Assessment of study quality

The methodological quality of the included studies was assessed using a 10-item checklist, which has been used by studies employing similar ALE meta-analytic methods to summarize functional and structural neuroimaging findings (Chen et al., 2015; Lai et al., 2021; Li et al., 2020; Zhu et al., 2022). This tool outlines the appraisal of demographic, neuroimaging, and reporting methods of individual studies, and was deemed most suitable based on the nature of the articles included in the present analyses. Items 1, 2 and 3 were modified to reflect the participants in the included studies, that is, healthy controls. See Supplementary Table 1 for the exact checklist used.

3. Results

3.1. Summary of search results

Following the removal of duplicates, the titles and abstracts of 14,168 studies were screened for inclusion in the present ALE meta-analyses (see Fig. 1). Ultimately, 52 articles were included in the final analyses (micturition, $n = 19$; swallowing, $n = 18$; blinking, $n = 6$; coughing, $n = 9$). See Supplementary Figs. 1–4 for individual PRISMA flowcharts for each behavioral domain. Overall, 825 participants were included in the final analyses (micturition, $n = 247$; swallowing, $n = 307$; blinking, $n = 106$; coughing, $n = 165$). The analyses comprised 876 foci of significant activation (micturition, $n = 145$; swallowing, $n = 360$; blinking, $n = 60$; coughing, $n = 311$). See Supplementary Tables 6–9 for all coordinates used in the analyses for each behavioral domain.

3.2. Summary of included studies

Tables 1–4 report behavior-specific study characteristic information. The studies included in the present ALE meta-analyses used various task-related fMRI, PET, and SPECT paradigms to contrast activation associated with the behaviors of interest to a control task, such as rest. Many of the included studies utilized behavioral paradigms to specifically examine activation associated with an urge for action, such as the suppression of micturition, normal blinking, or evoked coughing. However, some studies used paradigms that while not specifically assessing the urge for action, met our inclusion criteria and would likely be associated with urge-related brain activity, such as micturition, and swallowing (Jackson et al., 2011). That is, while these studies did not directly aim to examine the urge for action, such paradigms would likely activate regions involved in the control of the associated behavior (Blok, 1997; Jackson et al., 2011). Assessment of the quality of the included studies for each behavioral domain demonstrated that 38/52 studies were considered Good, and 14/52 Very Good quality. No studies were considered to be Low quality based on these criteria. Some of the studies included in the present ALE meta-analyses were limited by relatively small samples sizes, with 19/52 studies reporting on samples sizes of ≤ 10 participants. Additionally, not controlling for nuisance covariates (e.g., age and sex) also lowered the quality rating of some studies. See Supplementary Tables 2–5 for the quality scores for each included study.

3.3. Localizing a network for natural physiological urge

We performed ALE meta-analyses of task-related neuroimaging findings to assess which brain regions are consistently activated by the urge to micturate, swallow, blink, and cough. The analyses identified several regions commonly activated across all behavioral domains. Specifically, all physiological urges activated the right dorsal anterior-insular cortex, left inferior frontal gyrus (IFG), and right SMA, yet not the exact spatial location. Additionally, 3/4 behaviors showed activation in the right IFG, left dorsal anterior-insular cortex, and bilateral mid-/anterior- cingulate cortex. Further, 2/4 behaviors demonstrated activation in the left thalamus, SMA, and precentral gyrus, right

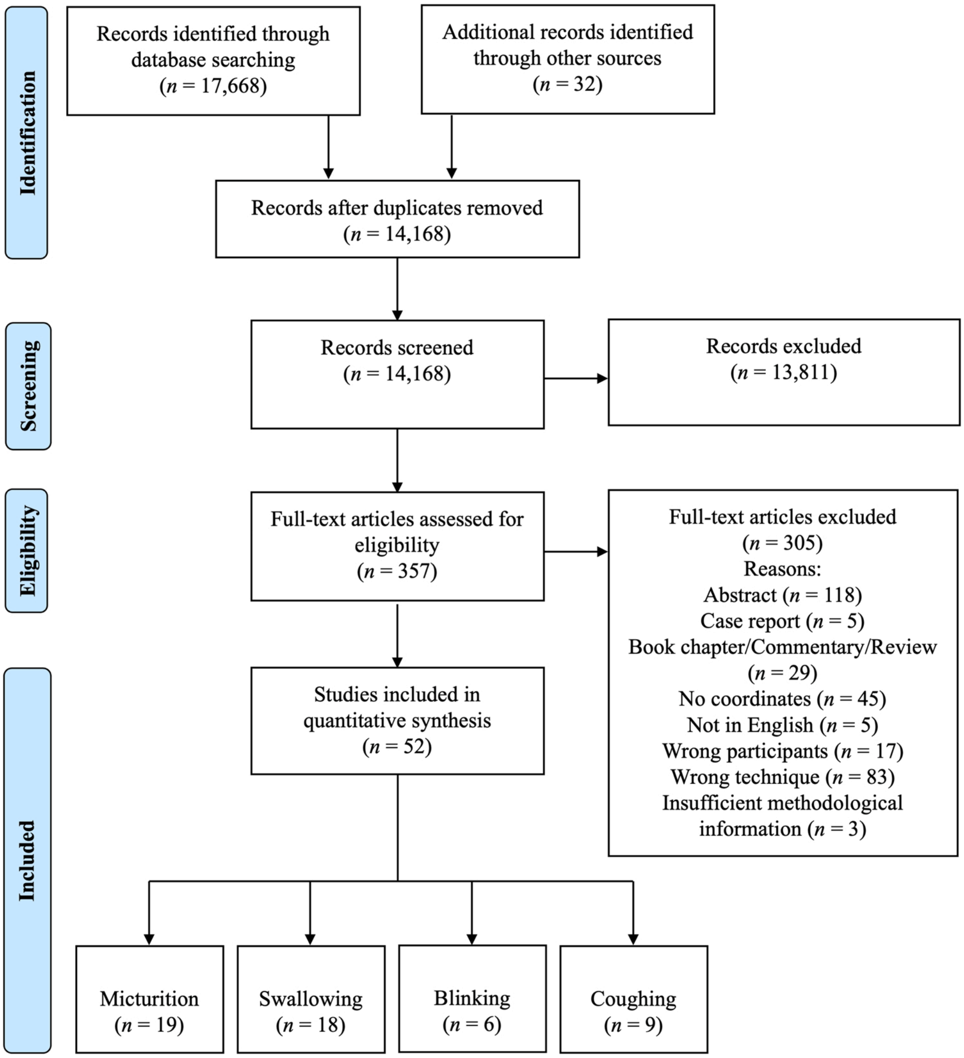

Fig. 1. Overall PRISMA Systematic Literature Search Decision Flowchart. PRISMA systematic search flowchart displaying the study inclusion process for the four systematic searches for the urge to micturate, swallow, blink, and cough combined. For individual PRISMA flowcharts for each behavioral domain, see Supplementary Figs. 1–4. Adapted from Moher et al. (2009).

postcentral gyrus, and bilateral claustrum. Together these regions activated by at least two of the behavioral domains comprise structures falling within our urge network (see Fig. 2). It should be noted that while these regions were similarly activated across all or most behavioral domains, this overlap was often not within the same exact voxel in the brain. Table 5 provides the exact xyz coordinates for where $\geq$2 behavioral domains overlapped for each brain region in the identified urge network. For a summary of the activation clusters identified by the ALE meta-analyses for each behavioral domain, see Supplementary Table 10.

3.4. Network similarity between the urge for action and Tourette syndrome

To examine which brain regions may be associated with the urge to tic in TS, we then examined the similarity between the identified urge network and the aforementioned TS network we previously localized using CNM (Zouki et al., 2023). These networks showed consistent activation in the left thalamus (xyz = −8, −18, 2). Network similarity was also identified in the left dorsal anterior-insula (xyz = −34, 14, −4) and right insula, however, the ventral anterior portion (xyz = 40, 16, −7). Interestingly, there was also direct overlap in the bilateral ACC (R xyz = 2, 24, 21; L xyz = −3, 24, 21), and left claustrum (xyz = −33, 9, −2) between the urge to cough network and the TS network (see Fig. 3). Therefore, these regions of network similarity may provide insight into the neural correlates of the premonitory urge to tic in TS patients.

4. Discussion

The present study utilized ALE meta-analysis to identify an urge network in healthy individuals common to the natural physiological behaviors of micturition, swallowing, blinking, and coughing. To assess neuroanatomical associations with the urge to tic in TS, we then examined which brain structures within this urge network are common to a network we previously localized in TS (Zouki et al., 2023). Our ALE meta-analyses identified a network of brain structures consistently activated by all or most of these four physiological behaviors, including the insula, claustrum, mid-/anterior- cingulate cortex, IFG, pre- and post-central gyri, thalamus, and SMA. We then demonstrated that several of these brain regions also fall within our TS network, including the bilateral insula, ACC, and left thalamus and claustrum. These findings may provide support for the role of urge-related brain regions in TS pathophysiology. Future neuroimaging studies examining the involvement of these brain regions during task-based urge paradigms will be helpful in clarifying the relative importance of these regions in TS. Historically, urge acceptance has not been a primary treatment focus in TS (Gev et al., 2016). Such findings may inform the potential importance

Table 1
Characteristics of studies included in the ALE analysis of the urge to micturate.

Study	Mean age ± SD (age range)	*N* (female)	Main task	Control task	Imaging	Design	*N* repetition	Bladder status	Bladder filling
Blok et al. (1997)	35 (22–50)	10 (0)	Micturition	Empty bladder	PET	Block	1	Full	Natural
Blok et al. (1998)	27 (20–51)	10 (10)	Micturition	Empty bladder	PET	Block	1	Full	Natural
Fukuyama et al. (1996)	28.2 ± 5.6 (22–37)	10 (0)	Micturition	Rest	SPECT	Block	1	Full	-
Griffiths et al. (2009)	(30–79)	10 (10)	Bladder filling	Bladder withdrawal	fMRI	Block	4–6	Full	Catheter
Krhut et al. (2014)	(20–68)*	19 (19)	Bladder filling	Bladder withdrawal	fMRI	Block	4	Full	Catheter
Kuhtz-Buschbeck et al. (2005)	24.5 ± 2.8 (20–29)*	17 (17)	Mimic micturition initiation	Suppress desire-to-void	fMRI	Block	5	Full	Natural
Kuhtz-Buschbeck et al. (2009)	26.4 ± 4.2	33 (17)	Mimic micturition initiation	Suppress desire-to-void	fMRI	Block	5	Full	Natural
Matsuura et al. (2002)	30 (24–41)	11 (0)	Urine withholding	Empty bladder	PET	Block	3	Full	Catheter
Mehnert et al. (2008)	24.3 (21–27)	8 (8)	Bladder filling	Rest	fMRI	Block	5	Full	Catheter
Michels et al. (2015)	26.2 (21–35)	14 (0)	Micturition	Rest	fMRI	Event-related	At least 8	Full	Natural
Nour et al. (2000)	23.4 ± 1.1 (22–25)	8 (0)	Micturition	Empty bladder	PET	Event-related	2–4	Full	Catheter
Seseke et al. (2006)	30.0 ± 6.9 (20–44)	11 (11)	Mimic micturition initiation	Suppress desire-to-void	fMRI	Block	15	Full	Natural
Seseke et al. (2008)	32.4 ± 7.9 (19–49)	12 (0)	Mimic micturition initiation	Suppress desire-to-void	fMRI	Block	15	Full	Natural
Shy et al. (2014)	32.4 (25–45)	10 (10)	Micturition	Rest	fMRI	Event-related	4	Full	Catheter
Tadic et al. (2013)	65.1 ± 4.2 (60–71)	11 (11)	Bladder filling (large bladder volume)	Bladder withdrawal	fMRI	Block	4–5	Full	Catheter
Takao et al. (2008)	(31–40)	6 (0)	Bladder filling (first desire-to-void)	Rest (post-voiding)	PET	Block	3	Full	Natural
Walter et al. (2019)	39.0 ± 12.0 (22–54)	20 (10)	Bladder filling	Rest (pre-filled bladder with 100 ml of water)	fMRI	Block	8	Full	Catheter
Walter et al. (2021)	28–44	12 (12)	Bladder filling	Rest (pre-filled bladder with 100 ml of water)	fMRI	Block	8	Full	Catheter
Yin et al. (2006)	32.7 ± 7.3 (24–45)	15 (0)	Urine withholding	Empty bladder	SPECT	Block	1	Full	-

Notes: PET = positron emission tomography; SPECT = single photon emission computed tomography; fMRI = functional Magnetic Resonance Imaging.
* = Based on initial sample before exclusion of participants; - = information unavailable. While not explicitly stated, it is suspected that the female participants reported on by Kuhtz-Buschbeck et al. (2009) are those from Kuhtz-Buschbeck et al. (2005).

Table 2
Characteristics of studies included in the ALE analysis of the urge to swallow.

Study (*N* experiments)	Mean age ± SD (age range)	*N* (female)	Main task	Control task	Imaging	Design	*N* swallows
Choi and Pyun (2021)	33.5 ± 7.6 (19–45)	15 (0)	Voluntary saliva swallowing	No swallowing	fMRI	Block	15
Fraser et al. (2002)	26 (23–34)	8 (1)	5 ml water swallowing	No swallowing	fMRI	Block	12
Hamdy et al. (1999)	48 (35–65)	8 (0)	5 ml water swallowing	Rest	PET	Block	-
Harris et al. (2005)	(29–37)	8 (0)	5 ml water swallowing	Rest	PET	Block	-
Huang et al. (2022)	56.2 ± 9.7 (40–80)	30 (19)	Voluntary saliva swallowing	Rest	fMRI	Block	5
Kober et al. (2019) (2)	29.2 ± 5.6	11 (7)	Voluntary saliva swallowing	Rest	fMRI	Event-related	-
			Covert swallowing	Rest		Event-related	NA
Li et al. (2009a) (2)	34.2 ± 8.1 (25–45)	10 (5)	Voluntary saliva swallowing	No swallowing	fMRI	Event-related	15
			3 ml water swallowing	No swallowing		Block	6
Li et al. (2009b)	70.3 ± 4.2 (65–75)	10 (5)	Voluntary saliva swallowing	No swallowing	fMRI	Event-related	15
Lowell et al. (2008) (2)	36 ± 10.4 (21–52)	14 (7)	Voluntary saliva swallowing	Rest	fMRI	Event-related	45
			Covert swallowing	Rest		Event-related	NA
Martin et al. (2001) (3)	28.0 ± 6.2*	12 (12)	Naïve swallowing	Rest	fMRI	Event-related	1–9
		14 (14)	Voluntary saliva swallowing	Rest		Event-related	4–12
		13 (13)	3 ml water swallowing	Rest		Event-related	5–17
Martin et al. (2004)	28.0 ± 6.5	14 (12)	Voluntary saliva swallowing	Rest	fMRI	Event-related	6
Martin et al. (2006) (2)	74.2 ± 8.1*	9 (9)	Voluntary saliva swallowing	Rest	fMRI	Event-related	8
		8 (8)	3 ml water swallowing	Rest		Event-related	
Moon et al. (2016)	(19–73)	30 (19)	Voluntary saliva swallowing	No swallowing	fMRI	Block	15
Park et al. (2017)	69.9 ± 4.9 (65–80)	10 (8)	3 ml water swallowing	No swallowing	PET	Block	-
Peck et al. (2010)	25 ± 2.5 (20–30)	10 (5)	Voluntary saliva swallowing	Rest	fMRI	Event-related	10
Shibamoto et al. (2007)	29.2 (23–38)*	19 (12)*	5 ml water swallowing	Rest	fMRI	Block	8
Suzuki et al. (2003)	(24–42)	11 (4)	Voluntary saliva swallowing	No swallowing	fMRI	Block	3
Zald and Pardo (1999)	30 (20–51)	8 (3)	Voluntary saliva swallowing	Rest	PET	Block	-

Notes: PET = positron emission tomography; fMRI = functional Magnetic Resonance Imaging;
* = Based on initial sample before exclusion of participants; NA= Not Applicable; - = information unavailable. Within parentheses is the number of experiments that contributed to the analysis for each study.

Table 3
Characteristics of studies included in the ALE analysis of the urge to blink.

Study (*N* experiments)	Mean age ± SD (age range)	*N* (female)	Main task	Control task	Imaging	Design	Main task duration	*N* repetitions
Berman et al. (2012) (3)	29.7 ± 7.9*	14 (8)	Blink suppression	Spontaneous blinking	fMRI	Block Event-related ’URGE’ model	60 s	3–6
Chung et al. (2006)	22 ± 1.5	12 (5)	Blink suppression	Voluntary blinking	fMRI	Event-related	20/25/30 s randomized	15
Kato and Miyauchi (2003)	26–48	7 (2)	Blink suppression	Spontaneous blinking	fMRI	Block	10 s	6
Lerner et al. (2009)	21–47	14 (7)	Blink suppression	Spontaneous blinking	PET	Block	60 s	3
van der Salm et al. (2018)	41.3	19 (9)*	Blink suppression	Spontaneous blinking	fMRI	Block	25 s	11
Yoon et al. (2005)	22 ± 1.5	12 (5)	Blink suppression	Eyes closed	fMRI	Block	15 s	6

Notes: PET = positron emission tomography; fMRI = functional Magnetic Resonance Imaging.
* = Based on initial sample before exclusion of participants. Within parentheses is the number of experiments that contributed to the analysis for each study. While not explicitly stated, it is suspected that Chung et al. (2006) and Yoon et al. (2005) involve the same participants, however, these were included as separate experiments due to the differences in paradigm and analysis methods used.

Table 4
Characteristics of studies included in the ALE analysis of the urge to cough.

Study (*N* experiments)	Mean age ± SD (age range)	*N* (female)	Main task	Main task stimulus	Control task	Main task duration	Imaging	Design	*N* repetition
Abubakar et al. (2021)	24.94 ± 4.39	16 (7)	Evoked cough	Highest concentration of capsaicin that could be inhaled without coughing	Saline	20 s	fMRI	Block	2 stimulus blocks x 3 scans
Ando et al. (2016)	40.0 ± 12.0	16 (9)	Evoked cough	One increment below the first dose to elicit uncontrolled coughing	Saline	24 s	fMRI	Block	8 stimulus blocks
Ando et al. (2019)	30.6 ± 12.3	16 (6)	Evoked cough	Highest concentration of capsaicin that could be inhaled without coughing	Saline	24 s	fMRI	Block	8 stimulus blocks
Farrell et al. (2012)	25.7 ± 2.1	16 (5)	Evoked cough	C2 (high capsaicin dose) + 2 increments below this (low capsaicin dose)	Saline	18 s	fMRI	Block	8 stimulus blocks
Farrell et al. (2014)	25.1 ± 8.4	17 (5)	Evoked cough	Two dose increments lower than the C2	Saline	18 s	fMRI	Block	-
Farrell et al. (2020)	24.4 ± 8.5	20 (12)	Evoked cough	Highest suppressible capsaicin for 24 s without coughing	Saline	24 s	fMRI	Block	3 stimulus blocks x 4 scans
Leech et al. (2013)	23.4 ± 6.6	17 (7)	Evoked cough	Highest concentration to evoke strong urge to cough without reflexive coughing	Normal air	16 s	fMRI	Block	2 stimulus blocks x 4 scans
Mazzone et al. (2007)	32.1 (24−47)	9 (5)	Evoked cough	Capsaicin dose immediately before the C2 dose	Saline	24 s	fMRI	Block	4 stimulus blocks x 3 scans
Mazzone et al. (2011) (2)	24.9 ± 8.0	19 (7)	Evoked cough Cough suppression	C2	Saline	-	fMRI	Event-related	3 stimulus blocks x 4 scans

Notes: fMRI = functional Magnetic Resonance Imaging; C2 = level of capsaicin required to elicit two spontaneous coughs; - = information unavailable. Within parentheses is the number of experiments that contributed to the analysis for each study. Some of the participants reported on by Farrell et al# (2012) were sourced from Mazzone et al# (2011). Some of the participants reported on in Farrell et al# (2014) were included in Farrell et al# (2012) and Mazzone et al# (2011).

of incorporating acceptance of premonitory urges into existing therapeutic interventions for TS (Franklin et al., 2011) to reduce aversion to these uncomfortable internal states, thereby decreasing distress and improving coping.

4.1. Localizing a network for natural physiological urge

Although everyday behaviors such as micturition, swallowing, blinking, and coughing are under partial or full volitional control in healthy individuals, they are often associated with a build-up of urge until the relevant action has been accomplished and typically cannot be suppressed indefinitely (Berman et al., 2012; Jackson et al., 2011). A previous study employing ALE meta-analysis highlighted several brain regions suggested to be involved in this urge for action thought to drive natural physiological behaviors (micturition, swallowing, yawning) as well as the urge to tic in TS, namely the insular and cingulate cortices (right insula and mid-cingulate) (Jackson et al., 2011). However, it remains unclear whether these are common to anatomically distinct natural physiological urges that are phenomenologically similar to simple motor and vocal tics, such as blinking and coughing (Jankovic, 2001). In this study, we applied ALE meta-analysis to functional neuroimaging studies investigating the urge to micturate, swallow, blink, and cough,

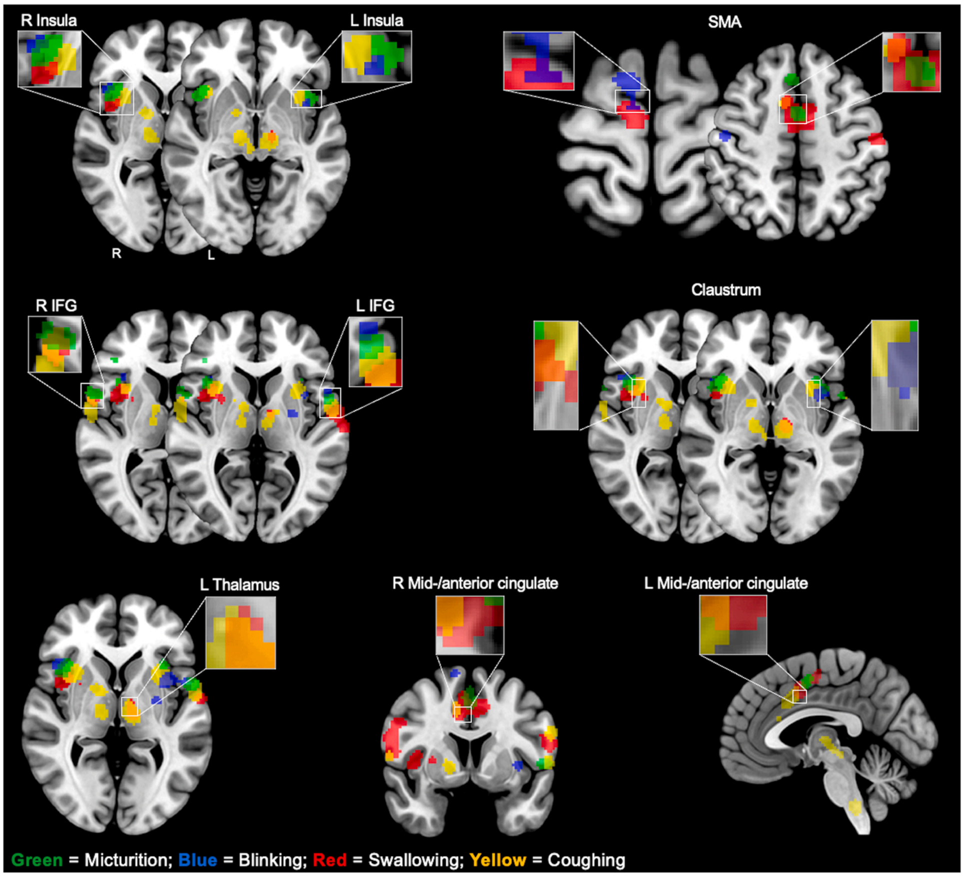

Fig. 2. Localizing a Network for Natural Physiological Urge. ALE meta-analysis results for the urge to micturate, swallow, blink, and cough overlaid onto the same brain slices. From left to right, these networks showed common activation in several cortical and subcortical regions, including the bilateral insula (z = 1, −4); SMA (z = 71, 51); IFG (z = 8, 6); claustrum (z = 4, −2); left thalamus (z = 2); and mid-/anterior- cingulate (R y = 4; L x = −3). Brain slices correspond to the coordinates listed in Table 5. While activation associated with individual behaviors was found in multiple additional brain regions, such as the basal ganglia, we defined the urge network as regions common to ≥2 behaviors. All slices shown in radiography view.

identifying a network of cortical and subcortical brain structures commonly activated by these physiological urges.

The right insula and mid-cingulate cortex are considered key hubs in the urge for action network, underlying the cognitive and sensory mechanisms of these processes (Berman et al., 2012; Jackson et al., 2021, 2011; Stern et al., 2020). Indeed, the bilateral insular and cingulate cortices are thought to serve as the ‘homeostatic/emotional/limbic sensorimotor neocortex’, providing adaptive (homeostatic) control of both the body and brain (for review see Strigo and Craig, 2016). This perspective aligns with evidence that feelings and awareness are generated by the insula, while motivations and agency are generated within the cingulate cortex (Strigo and Craig, 2016). Here, we found that all four physiological urges activated the right insula cortex. This is consistent with neuroimaging studies in healthy and clinical populations, such as TS and OCD, and lesion cases, suggesting that the insula is integral to interoception, the processing of bodily sensations, and choosing to act or withhold movement (Aziz et al., 1997; Brass and Haggard, 2010; Craig, 2003, 2002; Critchley and Harrison, 2013; Eickhoff et al., 2006; Ibañez et al., 2010; Stern et al., 2020). Similarly, we showed that all the included physiological behaviors commonly activated the left IFG. The left IFG, in addition to the right IFG, is implicated in behavioral and motor control in relation to externally and internally cued inhibition (Hirose et al., 2012; Schel et al., 2014; Swick et al., 2008). Many of the studies included in the four ALE meta-analyses used experimental paradigms which involved the suppression of the associated behavior, for example, the inhibition of evoked coughing to induce the urge to cough (Ando et al., 2019). Therefore, the consistent activation observed in the left IFG may be reflective of increased effort to control motor responses to the urge. Further, all the physiological behaviors showed activation in the SMA, albeit in different spatial locations. This structure has previously been implicated in action initiation and the urge for action (Potgieser et al., 2014; Stern et al., 2020). The SMA has rich connections to other cortical and subcortical regions, including the insula and thalamus (Behrens et al., 2003; Luppino et al., 1993; Potgieser et al., 2014), and is involved in motor circuits through its communication with the primary motor, premotor, and cingulate cortices (Luppino et al., 1993). Indeed, it has been demonstrated that electrical stimulation of the SMA in humans induces movement and the subjective ‘urge’ to perform movement (Fried et al., 1991).

While we showed that the urge to micturate, swallow, blink, and cough activated a common network of brain structures, the individual networks did not demonstrate exact anatomical convergence (see Results). Our inclusion criteria were based on several factors, including a previous ALE meta-analysis examining the urge for action (Jackson et al., 2011) and similarities between physiological urge and the subjective experience of premonitory urge as reported by patients with TS (Mazzone et al., 2011; van der Salm et al., 2018). However, although some of the studies included in each of the ALE meta-analyses were designed to measure the neural correlates of physiological urge, for example, involving the suppression of the associated behavior to increase urge intensity, some studies that met our inclusion criteria did not specifically aim to do this. Therefore, while we have attempted to choose the most appropriate paradigms that we expected would elicit an urge for action, it is possible that not all these experimental designs were optimized for measuring this phenomenon, which may account for the incomplete convergence demonstrated. Alternatively, it is possible that

Table 5
Coordinates corresponding to the natural physiological urge network.

Region (convergence %)	XYZ Convergence	Behavioral Domain
R dorsal anterior-insula (100)		
	40, 12, 1	Swallowing, coughing, micturition
	39, 19, 1	Blinking, coughing, micturition
L dorsal anterior-insula (75)		
	-38, 12, −4	Blinking, coughing,
	-38, 14, −4	Coughing, micturition
R SMA (100)		
	8, −10, 71	Swallowing, blinking
	5, 7, 51	Swallowing, coughing
	4, 6, 51	Swallowing, micturition
L SMA (50)		
	-5, −2, 51	Swallowing, micturition
R IFG (75)		
	59, 6, 8	Swallowing, coughing, micturition
L IFG (100)		
	-58, 5, 6	Micturition, coughing
	-60, 1, 6	Swallowing, coughing
	-54, 8, 6	Blinking, micturition
R Mid-/anterior- cingulate cortex (75)		
	2, 4, 43	Swallowing, micturition
	7, 4, 42	Swallowing, coughing
L Mid-/anterior- cingulate cortex (75)		
	-3, 8, 41	Swallowing, coughing
	-3, 4, 43	Swallowing, micturition
L Thalamus (50)		
	-8, −18, 2	Swallowing, coughing
R Claustrum (50)		
	32, 9, 4	Swallowing, coughing
L Claustrum (50)		
	-33, 9, −2	Blinking, coughing
L Precentral gyrus (50)		
	-58, −6, 37	Swallowing, coughing
R Postcentral gyrus (50)		
	62, −12, 23	Swallowing, coughing

Notes: Table 5 provides the exact xyz coordinates for where ≥2 behavioral domains overlapped for each brain region in the identified urge network and the percentage of behavioral domains that overlap within that brain region. Coordinates are presented in MNI (xyz) space. R = right; L = left; SMA = supplementary motor area; IFG = inferior frontal gyrus. Insula parcellations previously defined elsewhere (Deen et al., 2011).

while the voluntary suppression of these natural physiological behaviors, and tics alike, not only increases urge intensity, it may also alter the nature of the task or behavior and therefore the associated brain activity. Indeed, it has been suggested that the premonitory urge to tic may not be primary, rather secondary to the voluntary suppression of tics (for related discussion see van de Griendt et al., 2023; Jackson et al., 2020; Jackson et al., 2021).

4.2. Network similarity between the urge for action and Tourette syndrome

Premonitory urge is often described as the driving force behind tics (Bliss et al., 1980), therefore, uncovering the neural correlates of these sensory phenomena has been a growing research area over the last two decades (Cavanna et al., 2017; Draper et al., 2016). Previous research has suggested phenomenological and neurobiological similarities between premonitory urges in TS and the urges associated with everyday natural physiological behaviors (Cavanna et al., 2017; Jackson et al., 2011; Mazzone et al., 2010; Stern et al., 2020). In the present study, we provide some support for this proposal by directly examining similarity between a known network we previously localized in TS (Zouki et al., 2023), and networks associated with distinct natural physiological behaviors (micturition, swallowing, blinking, coughing), showing similar activation in several brain regions, including the bilateral insular cortex, ACC, and left thalamus and claustrum. Interestingly, while the urge to cough network and the TS network showed direct overlap in the ACC, overall, the identified 'urge network' primarily activated the mid-cingulate cortex, similar to the findings of Jackson et al. (2011). A recent study used structural neuroimaging methods to examine the involvement of three functionally defined regions of the cingulate cortex in TS symptomatology, namely the posterior mid-cingulate (pMCC), anterior mid-cingulate (aMCC), and posterior anterior cingulate (pACC) (Jackson et al., 2021). Of note, our TS network most closely aligns with the aMCC, while the urge network corresponds to the pMCC. The authors found that premonitory urge severity was uniquely positively correlated with a cluster of voxels in the aMCC, which may be consistent with this finding.

These common regions of activation have previously been implicated in the pathophysiology of tics in TS, including the premonitory urge to tic (Bohlhalter, 2006; Cavanna et al., 2017; Neuner et al., 2014). In a pivotal study using PET and a time-locked event-related paradigm to examine the neural correlates of tic generation, tic onset was associated with increased activation in several regions, including the SMA, insula, ACC, and basal ganglia (Stern et al., 2000). Replicating these findings, Lerner et al. (2007) reported activation in several cortical regions, including limbic areas (insula and ACC) and the SMA, during tic release. Using similar event-related designs and fMRI, several studies have demonstrated activation within the insula, ACC, and SMA prior to tic execution (Bohlhalter, 2006; Neuner et al., 2014). This functional activity preceding tic onset may be particularly relevant to the sensory phenomena thought to drive tics (Bohlhalter, 2006; Cavanna et al., 2017; Neuner et al., 2014). These potential functional correlates of premonitory urge are also supported by reports of structural alterations in patients with TS. For example, Draper et al. (2016) demonstrated that lower cortical thickness within the insula and sensorimotor network was associated with greater premonitory urge severity in young adult patients with TS. They also found lower cortical thickness within the sensorimotor cortices, anterior cingulate, and insula in these patients compared to their typically developed counterparts. These findings are consistent with an earlier structural MRI study, reporting lower grey matter volume in the ACC in patients with TS relative to matched controls (Draganski et al., 2010).

Contrary to previous research highlighting the role of the SMA in the premonitory urge to tic in TS, this structure was not a node within the TS network we previously localized using CNM (Zouki et al., 2023) and, therefore, was not a region of network similarity with the identified urge network. The role of the SMA remains unclear in TS, with it being implicated in both tic generation and the suppression of tics (Potgieser et al., 2014). Recently, He et al. (2022) found that lower SMA GABA+ (γ-aminobutyric acid + macromolecules) levels amongst children with TS were associated with greater premonitory urges, which are more frequent and severe, however, they did not find this association for the sensorimotor cortex or insula, which were also measured. Given that the posterior insula is functionally connected to the mid-cingulate region surrounding the SMA, the authors suggested that while premonitory urges are likely generated in the insula cortex, awareness of these urges may be partially mediated by tonic GABA levels in the SMA (He et al., 2022). Our present findings are not inconsistent with this proposal. The network we localized in TS was based on coordinates of structural alterations between patients with TS and healthy controls, therefore, it is possible that while anatomical abnormalities within the SMA may not be a neurobiological marker of TS, dysfunctional communication or compensatory mechanisms that occur between the SMA and focal hubs within the TS network are involved in the premonitory urge to tic. For example, greater structural connectivity was shown between the striatum and thalamus with the SMA in patients with TS relative to healthy controls, which was correlated with tic severity (Worbe et al., 2015). Similarly, Rae et al. (2020) argued that during tic suppression, the

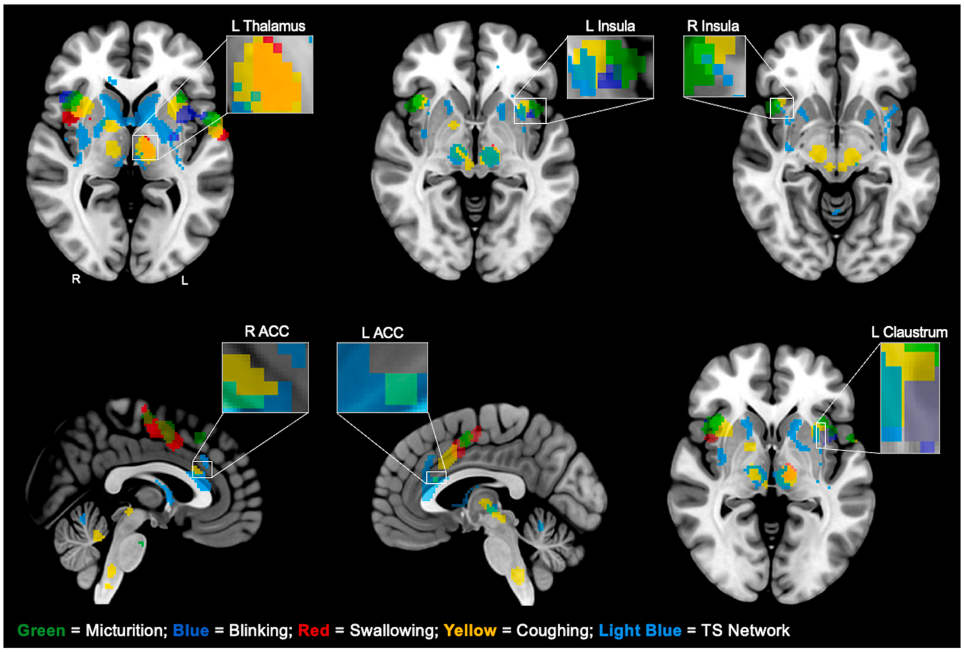

Fig. 3. Network Similarity Between the Urge for Action and Tourette syndrome. Regions of anatomical similarity between the urge and TS networks localized through ALE meta-analysis and CNM, respectively. These networks showed consistent activation in the left thalamus (z = 2), left dorsal anterior-insula (z = −4) and right insula, however, the ventral anterior portion (z = −7). There was also direct overlap in the bilateral ACC (R x = 2; L x = −3), and left claustrum (z = −2) between the urge to cough network and the TS network.

pre-SMA may communicate with subcortical regions, such as the sub-thalamic nucleus, to pause motor overflow i.e., tics. They further suggested that the pre-SMA is therefore not the site for primary neural dysfunction in TS, while the basal ganglia are implicated in tic genesis, which is consistent with our identified TS network.

Similarly, while not identified as a node in the present urge network in healthy individuals, the precuneus was identified as a key brain region in our TS network, being commonly connected to most coordinates of brain alterations in this population (Zouki et al., 2023). Previous neuroimaging findings have implicated activation of the precuneus in both premonitory urge severity and the suppression of tics in TS (Bhikram et al., 2021; Morand-Beaulieu et al., 2021), and given its role in self-awareness (Cavanna and Trimble, 2006), this region may represent a neural substrate of premonitory urge in TS (Zouki et al., 2023). It is possible that greater activation of the precuneus may be more specific to pathological urge. Alternatively, the precuneus may be more active during tasks that require conscious awareness of urge inhibition, for example, during the suppression of tics. Future functional neuroimaging investigations in TS patients that examine premonitory urge (e.g., tic suppression) will be valuable in deciphering the role of the precuneus in the urge to tic.

It should be noted that in the present study, we examined the similarity between two networks that were derived using different methods and populations. Specifically, we identified commonalities between a functional network for the urge for action derived from functional correlates in healthy individuals, using ALE meta-analysis, and a functional network derived from structural alterations in TS, using CNM. Importantly, our previously defined TS network was derived from samples of patients with a chronic tic disorder. Therefore, it is possible that these network regions may reflect brain alterations related to helpful adaptations to tic behaviors, or effects on the brain caused directly by chronic tics, rather than structures causally related to tics. However, these same brain regions (insula, ACC, thalamus) have also been implicated in networks derived from lesions causing tics, which provides support for their direct involvement in tic generation (Ganos et al., 2022; Zouki et al., 2023). We believe these methods were most appropriate for localizing the respective networks, however, further validation of these regions of similarity between the networks in TS patients is required. For example, we hypothesize that these regions of similarity (insula, ACC, thalamus) would be more active during high levels of the urge to tic in TS, therefore, these regions could be used as ROIs to examine activation during a task-based tic suppression paradigm in patients. Additionally, while we expected ALE to localize regions consistently activated by task-based functional neuroimaging studies, future studies could also assess the utility of CNM for summarizing such findings.

4.3. *Role of the urge for action network in the urge-tic-relief cycle*

The right anterior insula and mid-cingulate cortices are often referred to as the limbic sensory and motor areas respectively and are implicated in the neural mechanisms underlying the sensory and cognitive aspects of the urge for action (Jackson et al., 2011). These regions are suggested to be key nodes of the network that underlies the following functions: 1) represents visceral sensations and generates the urge for action; 2) selects the appropriate action associated with the urge based on a ‘cost-benefit’ analysis of the likely “value” the behavior will have in alleviating the urge; 3) stores evidence related to the outcome of the behavior; 4) assesses whether the action has alleviated the urge; and 5) where appropriate, generates the sensation of ‘urge-relief’ (Cavanna et al., 2017; Jackson et al., 2011). In the context of TS, it has been suggested that the cingulate may select or generate a particular behavioral or motor response to the premonitory urge that is primarily reflected by the anterior insula, while the consequence of the action as an urge relief is likely reflected by the mid-insular cortex (Jackson et al., 2021). Over time, this urge-tic-relief cycle becomes automatic and occurs outside of the individual’s awareness (Eapen and Usherwood, 2022; Leckman, 1993).

Exposure and response prevention (ERP) and habit reversal training (HRT) are considered the first-line treatments for mild-to-moderate tics, aiming to increase awareness of premonitory urges (Andrén et al., 2022). ERP involves exposure to premonitory urges while withholding the relief of tics, while HRT uses competing responses to prevent the expression of tics. There is strong evidence suggesting that the genesis of premonitory urge occurs within the insular and cingulate cortices (He et al., 2022; Jackson et al., 2021, 2011; Stern et al., 2020). However, changes in symptom severity in response to behavioral treatment through control over tics and/or tolerance of the premonitory urge to tic may involve other regions within the identified urge network, such as the thalamus. Supporting this hypothesis, the thalamus has extensive projections to limbic (e.g., ACC and insula) (Eckert et al., 2012; Van der Werf et al., 2002) and motor areas (globus pallidus and striatum) (Berendse and Groenewegen, 1991; Eckert et al., 2012; Jayaraman, 1985; Macchi et al., 1984), therefore is considered a viable target for neuromodulation interventions for tics (Jo et al., 2018). In a recent study employing deep brain stimulation and intra-operative fMRI during high-frequency stimulation in five patients with medically intractable tics, it was found that thalamic stimulation resulted in greater activity in the ACC and relatively reduced activity in the insular cortex, which was associated with reduced motor tic severity (Jo et al., 2018). Therefore, the authors suggested that thalamic stimulation may act through sensorimotor and insular cortices to modulate motor tics in response to premonitory urges. Studies examining functional network changes post-behavioral interventions will be useful in validating the role of this network in the modulation of the urge-tic-relief cycle.

Finally, in addition to the experience of internal sensory phenomena (premonitory urge), there is increasing evidence that patients with TS display a greater level of sensitivity to external stimuli (Cox et al., 2018), such as heightened sensitivity to tactile stimuli although showing normal sensory detection thresholds (Belluscio et al., 2011). Therefore, sensory processing disturbance has been suggested to be an important component of TS symptomatology (Tinaz et al., 2014; Friedrich et al., 2021). Several neural correlates have been proposed to underlie such sensorimotor processing deficits, including the sensorimotor cortex, thalamus/basal ganglia, and cortical areas related to salience of stimuli, such as limbic regions, including the insula (Tinaz et al., 2014). Our findings are consistent with this postulated neuropathology, however further research is required to decipher the neural mechanisms in TS.

5. Limitations

There are some limitations with the present study that should be acknowledged. First, a relatively small number of studies for the ALE meta-analyses of the urge to blink ($n = 6$) and cough ($n = 9$) met our inclusion criteria. Similarly, 19/52 studies included in the present ALE meta-analyses included ≤ 10 participants within their neuroimaging analyses. While there were several regions of consistency across the networks associated with all four physiological urges, future functional neuroimaging studies in healthy and clinical populations, employing larger samples sizes that account for important demographic variables, will be valuable in confirming the involvement of these regions in the urge for action. Second, ALE meta-analytic results are derived from the inclusion of significant coordinates of activation. The threshold of significance for these coordinates is dependent on the study design, such as image processing and the statistical analysis threshold applied, which is not uniform across individual papers. Ultimately, the optimal approach would be to extract peaks from the original unthresholded functional contrast maps from the published papers, yet these were not available to us. Future neuroimaging studies should consider making these maps publicly available. While the ALE meta-analysis algorithm can control for some of this variance contributed by methodological differences between studies, this is not accounted for entirely. Third, as previously mentioned above, there are differences in study paradigms within each behavioral domain, which may affect the extent to which these experiments measure urge phenomena. We attempted to account for this variability by choosing the study designs that we believed would optimize the measurement of the associated urge for action. Fourth, all participants within the studies included in our urge network analyses were >18 years old. Previous studies have found that functional networks may differ between adolescent and adult TS patients (Nielsen et al., 2020), therefore, it remains unclear whether these urge-related brain regions would show differential modulation during childhood compared to patients that have persistent tics into adolescence and adulthood. Finally, in the present study, we did not test for functional network correlates of premonitory urge phenomena in TS patients. Future studies examining functional connectivity between these regions in association with premonitory urge severity scores in patients with TS will be useful in disentangling the role of these regions in the urge to tic.

6. Conclusion

Using ALE meta-analysis, we identified an urge network common to natural physiological behaviors in healthy individuals. This network showed anatomical similarity with a network we previously localized in TS (Zouki et al., 2023), encompassing the bilateral insula, ACC, and left thalamus and claustrum. This novel approach supports previous neuroimaging investigations highlighting these structures as key nodes representing physiological urge for action and the premonitory urge to tic in TS (Cavanna et al., 2017; Jackson et al., 2021, 2011; Stern et al., 2020). Together, these findings highlight ROIs for future research evaluating the neural correlates of therapeutic change post-behavioral interventions targeting the urge to tic in TS. Such future finding may propose adjuncts to current effective behavioral interventions for TS to incorporate urge acceptance, rather than solely suppressing the urge to tic.

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Declaration of Competing Interest

The authors report no competing interest to declare regarding this work.

Data availability

Data available at NeuroVault link: https://neurovault.org/collections/GOKZXUGP/.

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Declarations of Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105779.

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