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Cognitive and motor event-related potentials in Tourette syndrome and tic disorders: A systematic review

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HIGHLIGHTS

- Event-related potentials offer a valuable insight into Tourette syndrome patients' brain activity.
- Most evidence points toward impaired motor-related and slow cortical potentials.
- Some differences in event-related potentials are attributable to comorbid disorders.

ABSTRACT

Objectives: Tourette syndrome (TS) patients face various cognitive and motor impairments. Event-related potentials (ERP) constitute an effective way to investigate the neural correlates of those functional impairments. Various components have been assessed among TS patients, with a wide variety of paradigms. This systematic review aimed to evaluate the portrait of ERP components in TS patients, and to understand the factors leading to discrepancies across studies.
Methods: A literature search was performed in Embase, PsycINFO, Pubmed, and Web of Science, to identify studies that conducted ERP experiments among TS patients. Of the 372 unique records identified, 47 met inclusion criteria and were included in our systematic review.
Results: Various ERP particularities were reported among included studies. Many discrepancies exist, but impairments in motor-related potentials and contingent negative variation seem constant across studies. Divergent findings point toward a possibly reduced P3b during oddball tasks.
Conclusions: ERPs offer an insightful investigation into the cognitive and motor functions of TS patients. Future studies should always control for confounding factors such as comorbidity, age, or medication status.
Significance: This is the first systematic review of ERP in TS patients. Motor-related and slow cortical potentials could constitute electrophysiological markers of TS.

1. Introduction

Tourette syndrome (TS) is a neurodevelopmental psychiatric disorder involving motor and phonic tics. Tics are conceptualized as involuntary motor contractions or vocalizations (American Psychiatric Association, 2013). These tics can be either simple or complex. Simple motor tics are the most frequent ones, and may take the form of eyeblinks, nose twitches, or head jerks, among others. While simple motor tics only involve one group of muscles, complex motors tics involve multiple groups of muscles in a coordinated sequence. Simple phonic tics, such as coughing, sniffing, or throat clearing, are also common among TS patients. While complex phonic tics such as coprolalia are often portrayed as the cardinal symptom of TS, they only affect a small proportion of patients. TS holds its name from the French neurologist George Gilles de la

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Tourette, who worked under the supervision of Jean-Martin Charcot at the Salpêtrière hospital in Paris. In 1885, Gilles de la Tourette described the cases of nine patients with motor and vocal tics, in what was the first systematic report of the disorder. The first half of the 20th century did not see major update on the pathophysiology of TS. During that time, TS was mostly explained and treated from a psychoanalytic standpoint (Ferenczi, 1921, Mahler et al., 1946). In the second half of the 20th century, the neurobiological etiology of TS became clearer, thanks to the discovery that haloperidol could decrease tic severity (Seignot, 1961, Shapiro et al., 1968). Despite these discoveries and the rise of new pharmacological treatments for TS, the neurological fundamental basis of tic generation was not well documented until recently. With new advances in neuroscience, the last decades revealed noteworthy and crucial clues in the understanding of the neurobiological etiology of that syndrome. It involves a miscommunication between the basal ganglia and the prefrontal cortex, through cortico-striato-thalamo-cortical (CSTC) loops (Mink, 2001). Such impairment is reflected in the altered activity of the frontal (Johannes et al., 2001a) and motor (Biswal et al., 1998) cortices. This impaired cerebral activity also has some impacts at the behavioral level, since patients face a wide range of motor (Abramovitch et al., 2017), cognitive (Eddy et al., 2009, Morand-Beaulieu et al., 2017b), and social (Eapen et al., 2016) impairments.

Many impairments were identified through relatively recent brain imaging data of TS patients obtained mainly from magnetic resonance imaging (MRI) or spectroscopy (MRS). Additionally, many researchers have used event-related potentials (ERP) to study the neural dynamics of motor and cognitive processes in TS patients. Given the cognitive and motor impairments characterizing TS, ERPs, which are based on the average EEG signal, constitute an effective method to understand the neural underpinnings of this condition. By averaging the EEG activity locked to a stimulus presentation or to the motor response, we can track the electrocortical activity associated with a given event with a high temporal precision. This procedure yields a series of components, identified according to their positive or negative polarity and their specific timing (latency in milliseconds). The ERP components (N200, P300, N400, lateralized readiness potentials (LRP), etc) are said to be endogenous components associated with the cognitive processing of the stimuli. These different components represent the real-time expression of various stages of information processing at the perceptual, cognitive, or motor level. The latency of ERP components and their sequence of occurrence allow a very precise tracking of cognitive processes timing, while their amplitude represent the allocation of neural resources to specific cognitive processes (Duncan et al., 2009). Therefore, ERPs offer an insightful investigation of cognitive and motor processes in TS. Yet, in comparison with other psychiatric disorders, such as schizophrenia or autism, ERPs have not been used extensively in the study of TS. Also, TS patients' ERPs have been elicited though various paradigms, therefore producing some discrepancies across studies. A systematic review has the potential to unravel these inconsistencies and yield a clearer picture regarding the situation of specific ERP components among TS patients.

A review of electrophysiological studies of TS was conducted by Orth (2010). This review only included five ERP studies, but reported frontal cortex impairments, differences in working memory process, and conflicting evidence regarding premotor potentials. To date, ERP studies including TS patients have not been exhaustively reviewed. Therefore, the goal of the current study was to systematically review ERP studies focusing on TS. Comorbid disorders will be considered, given their role in potentiating cognitive deficits in TS (Morand-Beaulieu et al., 2017a). This review will also investigate the possible role of pharmacotherapy or cognitive-behavioral therapy (CBT) on the ERPs of TS patients.

2. Methods

2.1. Literature search

A systematic search among the scientific literature of TS was first conducted in February 2018 and then updated in September 2018, using the Embase, PsycINFO, Pubmed, and Web of Science databases. The following keywords were used to retrieve relevant papers: (Tourette* OR tic OR tics) AND (event-related potentials OR event-related potential OR evoked potentials OR evoked potential OR bereitschaftspotential* OR readiness potential*). Manual search among the reference lists of included papers was also conducted to identify potentially relevant papers.

2.2. Study selection

To be included in the current systematic review, studies had to (1) be published in French or English in a peer-reviewed journal, (2) have recorded event-related potentials from scalp-EEG in an individual or a group of TS patients, and (3) included ERP relative to the presentation of a stimulus (visual or auditory) or to the production of a movement.

Study were excluded if (1) they had been retracted after publication, (2) they did not include patients with TS or a tic disorder, (3) they did not record cognitive or motor-related ERP (e.g. somatosensory-evoked, brainstem-evoked, motor-evoked, visually evoked potentials); and (4) if analyses were limited to the frequency or time-frequency domain.

Since this is the first systematic review on the ERPs of TS patients, we aimed to be as inclusive as possible. Each study fulfilling these criteria was included in the systematic review, whether they included a control group and whether they used an intervention or not. Also, studies were included regardless of their design. Given these parameters, a thorough assessment of the risk of bias within and across studies was not feasible.

2.3. Data extraction

The main outcome was the information on TS patients' ERPs, but the following data were also extracted: participants' demographics (age and sex), sample size, tic severity, comorbidity, medication, experimental task, behavioral performance, and ERP components assessed. Relevant information on TS patients' ERP were extracted from included papers and reported separately for each ERP component or category.

3. Results

3.1. Study characteristics

After the exclusion of duplicates, our literature search identified 372 studies, which were then screened for eligibility based on title and abstract. At this stage, 289 papers were excluded. The full-text of the remaining 83 studies was assessed for eligibility. Thirty-six studies were not eligible and were thus excluded. Therefore, 47 studies were included in our systematic review (see the PRISMA (Moher et al., 2009) flow diagram in Fig. 1). Demographic and clinical data of the patients in these studies are displayed in Table 1.

3.2. Component-specific results

Among TS patients, the most frequently assessed components were the P3b ($n = 26$), the P2 ($n = 11$), the N2 ($n = 14$), the N1 ($n = 8$), the BP ($n = 7$), the contingent negative variation ($n = 5$), and the error-related negativity ($n = 5$). Other event-related components were sparingly measured in TS patients, such as the P1,

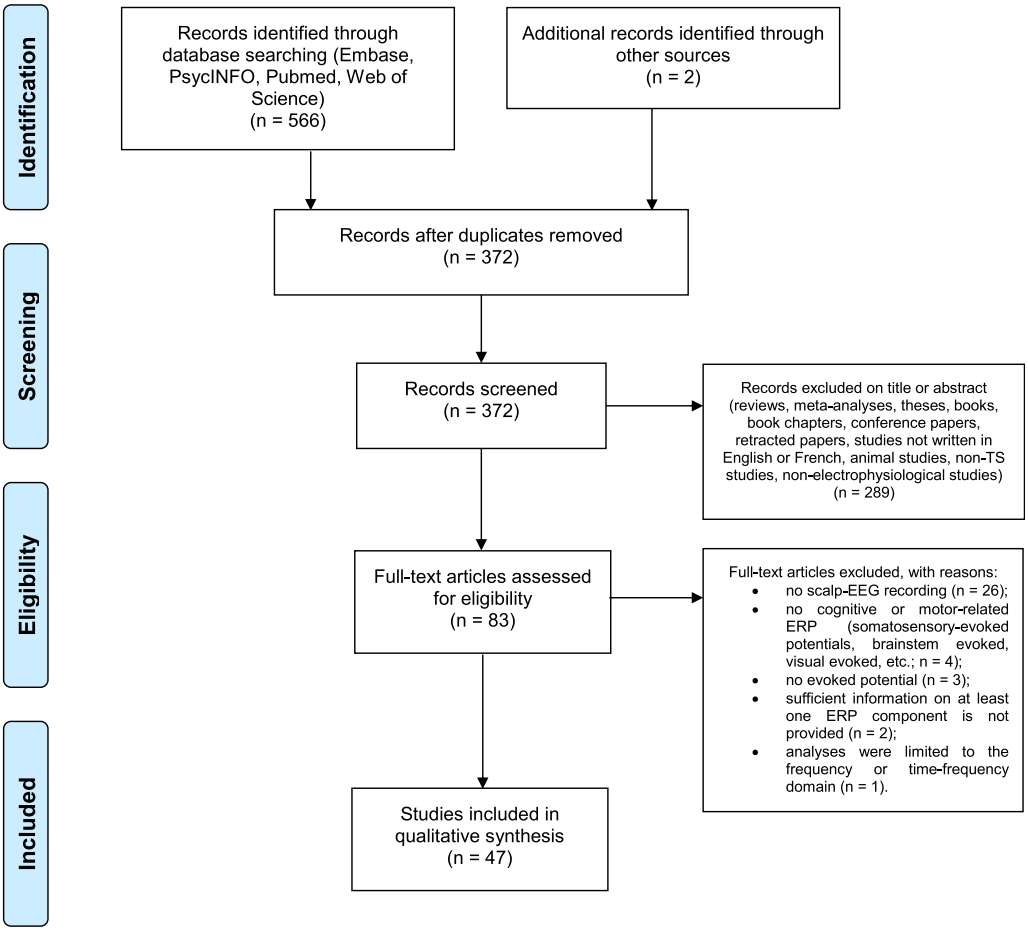

Fig. 1. Study selection flow chart. Selection process of the studies included in the systematic review, based on the PRISMA guidelines (Moher et al., 2009).

the N170, the mismatch negativity, and the lateralized readiness potentials, among others. Results of individual studies are summarized in Table 2.

3.2.1. P1

The P1 is mostly known to be elicited during visual tasks but can also be found in ERPs recorded during auditory paradigms. In the latter, it reflects sensory encoding of auditory stimulus attributes (Sharma et al., 1997). Its source is located around Heschl's gyrus (Godey et al., 2001). While it has not been studied extensively, the auditory P1 appears to be intact in TS patients (Surwillo, 1981; Oades et al., 1996; Brandt et al., 2017; Petruo et al., 2018).

The visual P1 reflects early processing of visual stimuli and can be modulated by attention or levels of arousal (Luck, 2005). Sources of the visual P1 are located in the middle occipital and fusiform gyri (Martínez et al., 1999). Following a visual stop stimuli in a stop-change task, the P1 was reduced in TS patients compared to healthy controls (Brandt et al., 2017). In a visual Simon task with emotional cues, children with TS showed shorter latencies of the P1 relative to anger cues, which suggests an early automatic encoding of anger in those patients (Kalsi et al., 2018). The authors also reported larger P1 amplitude over the right hemisphere regarding compatibility target-locked ERP.

3.2.2. N1

The N1 can be measured in both visual and auditory tasks. Like the P1, it reflects early attentional processes. It may also reflect some discriminative processes (Luck, 2005). Similar to the auditory P1, the auditory N1 has generators in Heschl's gyrus (Godey et al., 2001). The visual N1 is known to have generators in the fusiform gyrus (Herrmann et al., 2001).

The N1 has only been assessed a few times among TS patients, producing conflicting findings. In a single case study, Surwillo (1981) reported an intact N1 during an auditory paired-stimuli task. Yet, the character of this study limits its generalizability. In auditory oddball tasks, some oddball studies reported intact N1 latency (Drake et al., 1992; Oades et al., 1996) or amplitude (Oades et al., 1996), while other found decreased N1 amplitude (van de Wetering et al., 1985; van Woerkom et al., 1988a; van Woerkom et al., 1994). Intact visual N1 was found in a modified Eriksen-Flanker task (Eichele et al., 2016) or a Go/No-Go paradigm (Petruo et al., 2018). Yet, the N1 was reduced following visual stop stimuli in a stop-change task, but not following auditory change stimuli (Brandt et al., 2017).

Comorbidity could explain some part of the discrepancies, since TS+ADHD patients have been shown to have delayed N1 latency, when compared to TS-only patients (Drake et al., 1992). The inclusion of medicated patients could also be in cause, since pharmacological treatment allowed an increase of a diminished N1 in TS patients (van de Wetering et al., 1985).

3.2.3. Mismatch negativity and P165

The mismatch negativity (MMN) and the P165 component are obtained through a subtraction of targets from standards in auditory oddball tasks. They are part of a complex that also comprises the N2b and the P3b. Typically, a mismatching stimulus in an auditory oddball task will elicit a negative wave over central electrodes, which will peak around 200 ms (Luck, 2005). Yet, the overlap between the MMN, the P165, and the N2b can make the sole mea-

Table 1
Patients' demographic and clinical data.

Study	TS patients (n)	TS patients' characteristics							
		Mean age	Age range	Adults/ children	Sex ratio	YGTSS/ 50	YGTSS/ 100	Comorbidity	Medication
Bour et al. (2015)	3[x]	38.3	35–40	A	3 M:0F	43.7	N.R.	1 patient had a comorbid disorder: 1 TS+MDD.	All patients were under medication: clonidine (n = 1), pimozide+citalopram (n = 1), haloperidol+risperidone +oxazepam (n = 1).
Brandt et al. (2017)	15	30.4	N.R.	A	10 M:5F	19.3	34.3	5 patients had comorbid disorders: 2 TS +ADHD, 3 TS+OCD.	Six patients were under medication: aripiprazole (n = 2), carbamazepine (n = 1), methylphenidate (n = 1), paroxetine (n = 1), aripiprazole +pimozide (n = 1).
Chen and Chen (1997)	31	9.7	6–11	C	31 M:0F	N.R.	N.R.	N.R.	N.R.
Drake et al. (1992)	20	N.R.	8–20	C	15 M:5F	N.R.	N.R.	16 patients had comorbid disorders: 10 TS +ADHD, 6 TS+OCD. Data reported separately.	10 patients were under medication (haloperidol, pimozide, desipramine, and clonidine) but stopped their treatment at least one week before the study.
Duggal and Nizamie (2002)	3	30.7	16–51	Both	3 M:0F	N.R.	N.R.	2 patients had comorbid disorders: 2 TS+OCD. The other patient had subclinical OCD symptoms.	N.R.
Dumais-Huber and Rothenberger (1992)	13	11.6	8–15	C	13 M:0F	N.R.	N.R.	N.R.	Patients were not under medication during the study.
Eichele et al. (2016)	25	9.9	8–12	C	17 M:8F	19.3	N.R.	The following comorbidities were reported among the TS group: ADHD (n = 14), elimination disorder (n = 3), general anxiety (n = 1), phobia (n = 3), OCD (n = 2), ODD (n = 7), separation anxiety (n = 1). Data reported separately for TS and TS+ADHD patients.	All patients were medication-naïve.
Eichele et al. (2017)	17	14.2	11–17	C	11 M:6F	14.5	N.R.	The following comorbidities were reported among the TS group: ADHD (n = 10), anxiety disorder (n = 1), MDD (n = 1), phobia (n = 3), OCD (n = 3), ODD (n = 2), Data reported separately for TS and TS+ADHD patients.	2 patients were under medication: antipsychotic +melatonin (n = 1), antiepileptic (n = 1). 4 TS+ADHD patients were asked to stop their stimulant medication 48 hours prior to testing.
Hanna et al. (2012)	9[y]	13.6	10–19	C	6 M:3F	N.R.	N.R.	One patient had a history of ADHD.	Individual medication was not reported, but patients under medication other than SSRI were excluded from the study.
Howson et al. (2004)	14	12.1	8–17	C	12 M:2F	20.9[a]	N.R.	12 patients had comorbid disorders: TS+ADHD (n = 6), TS+OCS (n = 1), TS+ADHD+OCS (n = 2), TS+ADHD+Aspergers (n = 1), TS+ADHD+OCS +LD (n = 1), TS+ADHD+OCS+LD+CD (n = 1).	All patients were under medication: haloperidol (n = 4), haloperidol+methylphenidate+trazodone (n = 1), pimozide+clonidine (n = 1), pimozide+risperidone (n = 1), pimozide+clonidine+methylphenidate (n = 1), pimozide+clonidine+dextroamphetamine+paroxetine (n = 1), risperidone (n = 1), risperidone +methylphenidate (n = 1), risperidone+clonidine +dextroamphetamine (n = 2), risperidone +dextroamphetamine+fluoxetine (n = 1).
Johannes et al. (1997)	12	32.9	18–62	A	12 M:0F	N.R.	N.R.	All patients had comorbid disorders: 9 TS+OCD, 3 TS+ADHD+OCD.	5 patients were under pimozide treatment.
Johannes et al. (1999)	12	32.9	18–62	A	12 M:0F	N.R.	N.R.	All patients had comorbid disorders: 9 TS+OCD, 3 TS+ADHD+OCD.	5 patients were under pimozide treatment.
Johannes et al. (2001a)	10	34.4	16–64	A	9 M:1F	N.R.	N.R.	5 patients had comorbid disorders: 2 TS +ADHD, 2 TS+OCD, 1 TS+ADHD+OCD.	4 patients were under neuroleptic treatment.
Johannes et al. (2001b)	10	34.4	16–64	A	9 M:1F	N.R.	N.R.	5 patients had comorbid disorders: 2 TS +ADHD, 2 TS+OCD, 1 TS+ADHD+OCD.	4 patients were under neuroleptic treatment.
Johannes et al. (2002)	10	34.4	16–64	A	9 M:1F	N.R.	N.R.	5 patients had comorbid disorders: 2 TS +ADHD, 2 TS+OCD, 1 TS+ADHD+OCD.	4 patients were under neuroleptic treatment.
Johannes et al. (2003)	10	34.4	16–64	A	9 M:1F	N.R.	N.R.	5 patients had comorbid disorders: 2 TS +ADHD, 2 TS+OCD, 1 TS+ADHD+OCD.	4 patients were under neuroleptic treatment.
Kalsi et al. (2018)	10	10.5	8–13	C	8 M:2F	17	N.R.	The following comorbidities were reported among the TS group: ADHD (n = 1), generalized anxiety disorder (n = 2), OCD (n = 1).	All patients were medication-naïve.

Karp et al. (1996)	5	34.0	22–56	A	4 M:1F	N.R.	N.R.	N.R.	Patients were not under medication during the study.
Lange et al. (2017)	23	32.8	N.R.	A	13 M:10F	22.5	45.6	4 patients had comorbid disorders: 1 TS +ADHD, 3 TS+OCD.	8 patients were under medication: aripiprazole: (n = 3), citalopram (n = 1), sertraline (n = 1), agomelatine (n = 1), methylphenidate (n = 1), risperidone (n = 1), tetrahydrocannabinol (n = 1).
Lavoie et al. (2011)	10	40	N.R.	A	7 M:3F	N.R.	N.R.	The following comorbidities were reported among the TS group: generalized anxiety disorder (n = 1), OCD (n = 2), specific phobia (n = 1).	3 patients were under medication: risperidone (n = 2), venlafaxine (n = 1).
Morand-Beaulieu et al. (2015)	20	38.0	19–61	A	13 M:7F	20.9	42.3	8 patients had comorbid disorders: 1 TS +ADHD, 1 TS+MDD, 5 TS+social anxiety disorder, 1 TS+panic disorder.	6 patients were under medication: clonazepam (n = 1), clonidine (n = 1), escitalopram (n = 1), paroxetine +lorazepam+risperidone (n = 1), salbutamol+venlafaxine (n = 1), zopiclone+citalopram (n = 1).
Morand-Beaulieu et al. (2016)	26	37.8	19–61	A	17 M:9F	20.6	40.2	8 patients had comorbid disorders: 1 TS +ADHD, 1 TS+MDD, 5 TS+social anxiety disorder, 1 TS+panic disorder.	7 patients were under medication: clonazepam (n = 2), clonidine (n = 1), escitalopram (n = 1), paroxetine +lorazepam+risperidone (n = 1), salbutamol+venlafaxine (n = 1), zopiclone+citalopram (n = 1).
Morand-Beaulieu et al. (2018)	26	37.8	19–61	A	17 M:9F	20.6	40.2	8 patients had comorbid disorders: 1 TS +ADHD, 1 TS+MDD, 5 TS+social anxiety disorder, 1 TS+panic disorder.	7 patients were under medication: clonazepam (n = 2), clonidine (n = 1), escitalopram (n = 1), paroxetine +lorazepam+risperidone (n = 1), salbutamol+venlafaxine (n = 1), zopiclone+citalopram (n = 1).
Oades et al. (1996)	10	11.7	8–15	C	9 M:1F	N.R.	N.R.	Individual comorbidities are not reported, but high Conner's ADHD scale scores were reported.	4 patients were under medication: pimozide (n = 2), tiapride (n = 2).
Obeso et al. (1981)	6	26.2	14–38	Both	6 M:0F	N.R.	N.R.	N.R.	N.R.
O'Connor et al. (2001)	29	N.R.	N.R.	A	N.R.	N.R.	N.R.	N.R.	N.R.
O'Connor et al. (2005)	13	39.5	N.R.	A	5 M:8F	N.R.	N.R.	Patients did not have significant comorbidity.	Patients were not under medication during the study.
Petruo et al. (2018)	35	13.0	9–19	C	29 M:6F	19.0	39.0	The following comorbidities were reported among the TS group: ADHD (n = 3), OCD (n = 11).	11 patients were under medication: tiapride (n = 3), aripiprazole (n = 3), methylphenidate (n = 3), and fluoxetine (n = 2).
Rothenberger et al. (2000)	11	12.1	N.R.	C	11 M:0F	N.R.	N.R.	All patients had comorbid ADHD.	Patients were either medication-naïve or were drug-free for at least 4 weeks prior to testing.
Sauvé et al. (2017)	12	33.0	19–47	A	7 M:5F	19.6	34.6	Comorbid patients were excluded.	Patients were not under medication during the study.
Schuller et al. (2018)	15	28.6	N.R.	A	12.3	22.5	47.2	No comorbidity is reported, but 4 patients showed high BDI scores without fulfilling the MDD criteria.	11 patients were under medication before the study: aripiprazole (n = 5), tiapride (n = 3), risperidone (n = 1), quetiapine (n = 1), pregabalin (n = 1), fluoxetine (n = 1). Medication was stopped 24 h before testing.
Shephard et al. (2016a)	34[1]	12.8	9–17	C	29 M:5F	23.7[b]	N.R.	17 TS-ADHD & 17 TS+ADHD. Data reported separately. Comorbidity among groups: TS-ADHD: OCD (n = 3), OCB (n = 4), MDD (n = 3), anorexia (n = 1); TS+ADHD: OCD (n = 2), ODD (n = 5), generalized anxiety (n = 2), social phobia (n = 2), specific phobia (n = 2), separation anxiety (n = 2), dyslexia (n = 1).	6 TS-ADHD patients were under medication: clonidine (n = 2), aripiprazole (n = 2), fluoxetine (n = 1), and citalopram (n = 1). 6 TS+ADHD were under medication: clonidine (n = 1), methylphenidate (n = 2), aripiprazole (n = 2), and fluoxetine (n = 1). Methylphenidate was stopped 24 h before testing, all other medications were continued.
Shephard et al. (2016b)	35[2]	12.8	9–17	C	30 M:5F	23.5[c]	N.R.	18 TS-ADHD & 17 TS+ADHD. Data reported separately. Comorbidity among groups: TS-ADHD: OCD (n = 3), OCB (n = 5), MDD (n = 3), anorexia (n = 1), anxiety disorder (n = 1); TS +ADHD: OCD (n = 2), ODD (n = 5), generalized anxiety (n = 2), social phobia (n = 2), specific phobia (n = 2), separation anxiety (n = 2), dyslexia (n = 1).	5 TS-ADHD patients were under medication: aripiprazole (n = 1), clonidine (n = 2), fluoxetine +clonidine (n = 1), and citalopram (n = 1). 5 TS+ADHD were under medication: clonidine+methylphenidate (n = 1), methylphenidate (n = 1), aripiprazole (n = 2), and fluoxetine (n = 1). Methylphenidate was stopped 24 h before testing, all other medications were continued.
Siniatchkin and Kuppe (2011)	7	12.6	*n*.R.	C	4 M:3F	N.R.	N.R.	Comorbid patients were excluded.	Individual medication was not reported, but patients did not change medication during the study.
Surwillo (1981)	1	13	N/A	C	1 M:0F	N.R.	N.R.	N.R.	ERP were recorded before and after haloperidol treatment.
Tijssen et al. (1999)	3[3]	N.R.	N.R.	A	1 M:2F	N.R.	N.R.	2 patients had comorbid panic disorder.	1 patient was effectively treated with tetrabenazine, but effective pharmacological treatment was not reported in other patients.

(*continued on next page*)

Table 1 (*continued*)

Study	TS patients (n)	TS patients' characteristics							
		Mean age	Age range	Adults/ children	Sex ratio	YGTSS/ 50	YGTSS/ 100	Comorbidity	Medication
Thibault et al. (2008)	26	34.8	N.R.	A	16 M:10F	N.R.	N.R.	12 patients had comorbid OCS. Data reported separately.	6 TS+OCD patients were under medication: risperidone (n = 1), pimozide+topiramate (n = 1), paroxetine +lorazepam+risperidone (n = 1), bromazepam (n = 1), citalopram+quetiapine (n = 1), bupropion+paroxetine (n = 1).
Thibault et al. (2009)	15	37.0	21–54	A	8 M:7F	N.R.	N.R.	Axis 1 diagnoses (other than TS) were excluded, but there is no explicit mention that ADHD or OCD is excluded.	Patients were unmedicated. 6 patients had been medicated in the past: SSRI (n = 1), benzodiazepine (n = 1), tretrabenazine (n = 1), haloperidol & tetrabenazine (n = 1), medication not specified (n = 2).
van de Wetering et al. (1985)	6	27.7	17–47	A	6 M:0F	N.R.	N.R.	4 patients had comorbid OCS. Also, 4 patients had LD in school, suggesting possible ADHD.	All patients were under medication: clonidine (n = 1), pimozide (n = 5).
van der Salm et al. (2012)	14	34.0	21–65	A	12 M:2F	N.R.	N.R.	4 patients had comorbid disorders: TS+ADHD (n = 1), TS+OCD (n = 3).	1 TS+ADHD patient was under methylphenidate treatment during the study.
van Woerkom et al. (1988a)	20	27.0	17–43	A	18 M:2F	N.R.	N.R.	N.R.	3 patients were under pimozide treatment during the study. Other patients were tested prior to their pharmacological treatment.
van Woerkom et al. (1988b)	18	23.0	N.R.	A	N.R.	N.R.	N.R.	10 patients had comorbid OCS.	2 patients were under pimozide treatment during the study.
van Woerkom et al. (1994)	53	19.1[d]	N.R.	Both	N.R.	N.R.	N.R.	N.R.	Patients were not under medication during the study.
Weate et al. (1993)	12	N.R.	10–21	C	10 M:2F	N.R.	N.R.	The following comorbidities were reported among the TS group (past or present): ADHD (n = 10), OCD (n = 3). Data reported separately.	3 patients had past treatment with haloperidol or diazepam, but all patients were drug-free during the study.
Yordanova et al. (1996)	22	12.5	N.R.	C	N.R.	N.R.	N.R.	11 patients had comorbid ADHD. Data reported separately.	Patients were either medication-naïve or were drug-free for at least 4 weeks prior to testing.
Yordanova et al. (1997)	22	12.5	N.R.	C	N.R.	N.R.	N.R.	11 patients had comorbid ADHD. Data reported separately.	Patients were either medication-naïve or were drug-free for at least 4 weeks prior to testing.
Zhu et al. (2006)	34	11.1	10–14	C	28 M:6F	N.R.	N.R.	15 patients had comorbid ADHD. Data reported separately.	Patients were not under medication during the study.

ADHD: attention deficit hyperactivity disorder, LD: learning difficulties, MDD: major depressive disorder, N/A: not applicable, N.R.: not reported, OCB: obsessive-compulsive behaviors, OCD: obsessive-compulsive disorder, OCS: obsessive-compulsive symptoms, ODD: oppositional defiant disorder, TS: Tourette syndrome.

[a] YGTSS data was calculated as the mean total tic severity score prior to placebo and nicotine conditions.

[b] YGTSS total tic score was 19.3 in TS-ADHD and 28.1 in TS+ADHD patients, with a significant difference between groups.

[c] YGTSS total tic score was 19.1 in TS-ADHD and 28.1 in TS+ADHD patients, with a significant difference between groups.

[d] TS children had a mean age of 12.5 years old and TS adults had a mean age of 27.0 years old.

Table 2
Overview of ERP studies in TS.

Study	TS patients (n)	Healthy controls (n)	Experimental task/condition	Behavioral results	Components assessed	ERP results
Bour et al. (2015)	3[a]	0	Spontaneous tics & voluntary imitation of tics	N.R.	BP	The BP was only measured in one patient, in which voluntary imitation of tics was preceded by a premotor potential, but not spontaneous tics.
Brandt et al. (2017)	15	15	Stop-change task	Stop-change condition: TS patients more accurate in the SCD-0 condition. Go condition: TS patients slower than HC.	P1, N1, P3b	Following visual stop stimuli, the P1 and N1 were smaller in TS patients, but they were not impacted by the stop-change delay. The P3b was smaller in immediate change trials in TS patients, which is hypothesized to represent a better multi-sensory integration during response selection processes.
Chen and Chen (1997)	31	0[b]	Visual oddball: counting and motor responses	N.R.	P3b	During the motor oddball task, children with TS had lower P3b amplitude than children with transient tics. However, both group showed similar P3b amplitude during the counting oddball task.
Drake et al. (1992)	20	20	Auditory counting oddball task	N.R.	N1, P2, N2, P3b	There was no difference between TS patients and HC regarding N1, P2, N2, and P3b latencies. TS+ADHD patients had longer N1 and N2 latencies than TS-only patients. TS+OCD patients had shorter P3b latencies than TS-only patients.
Duggal and Nizamie (2002)	3	0	Spontaneous tics	N/A	BP	All patients presented a BP prior to tic onset. The BP onset latency was shorter than that is usually observed in HC performing voluntary movements.
Dumais-Huber and Rothenberger (1992)	13	15	S1-S2 paradigm	TS patients were slower than HC in the non-control condition.	Early and late CNV, PINV	The early CNV in the control condition tended to be smaller in TS children, but there was no between-group difference regarding the late CNV and the PINV.
Eichele et al. (2016)	25	35	Modified Eriksen-Flanker task	No group difference regarding RT. No major group difference regarding accuracy, but higher incompatible error rates in TS patients.	Stimulus-locked: N1, P2, P3a, P3b/LPC. Response-locked: LPC, ERN, Early positivity, Pe	Stimulus-locked: No group difference regarding N1, P2, and P3b/LPC. P3a amplitudes were larger in TS patients, compared to HC and ADHD patients. Response-locked: No group difference regarding ERN, early positivity, and Pe. Larger LPC in TS patients when compared to HC.
Eichele et al. (2017)	17	29	Modified Eriksen-Flanker task	No group difference regarding RT. Group difference regarding accuracy were no longer significant at second assessment.	Stimulus-locked: P2, P3a, P3b/LPC. Response-locked: ERN, Pe	Stimulus-locked: No group difference regarding P2 and P3b/LPC. Group difference between TS patients and HC regarding P3a amplitudes were no longer significant at the second assessment. Response-locked: No difference between HC and TS patients regarding ERN and Pe.
Hanna et al. (2012)	9[c]	44	Modified Eriksen-Flanker task	No group difference regarding accuracy or RT.	ERN	Tic-related OCD patients did not differ from HC regarding ERN amplitude. Yet, these two groups showed smaller ERN amplitudes than non-tic-related OCD patients.
Howson et al. (2004)	14	0	Continuous performance task	No differences in RT or accuracy were observed following nicotine treatment relative to placebo.	P3b	There was a decrease in P3b amplitude in the placebo condition over a two-week interval, while the nicotine treatment allowed the P3b amplitude to remain stable.
Johannes et al. (1997)	12	12	Visual oddball task with motor responses, pop-out expertiment, figure extraction and figure conjunction paradigms	Hit rates were slower in TS patients, only during the figure conjunction paradigm. No group difference regarding RT on any of the 4 tasks.	N2, P3b	Oddball task (target stimuli): Larger N2 and smaller P3b in TS patients. Pop-out experiment: at frontal electrodes, TS patients showed larger N2 for target stimuli. Figure extraction paradigm: no difference between groups. Figure conjunction paradigm: Longer P3b latencies for TS patients.
Johannes et al. (1999)	12	12	Emotional word recognition paradigm	No group difference regarding hit rates. Trend toward slower RT in TS patients.	N400	For emotionally neutral words, TS patients and HC showed similar N400 old-new effect. For negative and positive words, the N400 old-new effect was larger in HC than in TS patients.
Johannes et al. (2001a)	10	10	Stop experiment, visual oddball task with motor responses	No group difference regarding accuracy or RT.	N2, No-Go Anteriorization, P3b, LRP	Stop experiment: Frontal shift of the NGA in TS patients. No group difference regarding LRP onset latency. TS patient had larger negativity during the 100–400 ms interval, suggesting a possibly enhanced N2. Oddball task: No group difference regarding P3b amplitude or latency.

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Table 2 (*continued*)

Study	TS patients (n)	Healthy controls (n)	Experimental task/condition	Behavioral results	Components assessed	ERP results
Johannes et al. (2001b)	10	10	Dual task experiment (detection of visual and auditory targets)	TS patients: impaired detection of auditory target when presented with high-difficulty visual targets.	P3b	In comparison with HC, TS patients had lower P3b amplitude for auditory than for visual ERPs, which suggest that allocation of resources to competing tasks is altered.
Johannes et al. (2002)	10	10	Visual oddball task with motor responses	No group difference regarding accuracy or RT.	ERN, P3b	The amplitude of the ERN was larger in the TS group. The latency of the ERN appeared to be longer also, but not statistically different from HC. No group difference regarding P3b amplitude or latency.
Johannes et al. (2003)	10	10	Stroop paradigm	No group difference regarding accuracy or RT.	N2, P3b, N450	The N450, which is maximally elicited by incongruent Stroop trials, was larger and had a longer latency in TS patients. Globally, the N2 component did not differ between TS and HC, but TS showed a hemispheric asymmetry that was not seen in HC. The P3b did not differ between TS and HC.
Kalsi et al. (2018)	10	10	Simon task with emotional clues	TS patients had lower accuracy in anger trials but did not differ from HC in other conditions.	P1, N170, first and second late components (LC1 & LC2)	Emotional cues ERPs: For anger cues, TS patients showed a shorter latency of the P1 and N170. Simon task target ERPs: TS patients showed increased frontal and central N170, LC1, and LC2. The N170 latency was also shorter in TS patients.
Karp et al. (1996)	5	0	Spontaneous tics & voluntary imitation of tics	N/A	BP, NS'	Premotor potentials were present before tic onset in two of the five patients. In one of them, the early BP could not be identified, but the NS' obtained during spontaneous tics was similar to the NS' obtained during voluntary movements.
Lange et al. (2017)	23	26	Computerized Wisconsin Sorting Card Test	No group difference regarding accuracy. TS patients were slower than HC.	P3b	TS patients showed higher parietal P3b activity during cue-locked trials.
Lavoie et al. (2011)	10	14	Traffic light test	N.R.	MP	Smaller go-stop amplitude difference in TS patients compared to HC in the automated response condition, mainly over the left hemisphere. Tic severity was positively correlated to the MP amplitude related to motor inhibition. CBT induced a normalization of motor cortical activation.
Morand-Beaulieu et al. (2015)	20	20	Stimulus-response compatibility paradigm	No group difference regarding accuracy or RT.	P3b, LPC, LRP	No group difference on the P3b. The frontal LPC had a higher amplitude and was delayed in TS patients, and the therapy had no impact on this component. The sLRP onset were delayed and the rLRP peak was higher in TS patients, when compared to HC. The sLRP onset accelerated and the rLRP peak decreased following CBT.
Morand-Beaulieu et al. (2016)	26	27	Visual oddball task with motor responses & visual counting oddball task	No group difference regarding accuracy or RT.	P2, N2, P3b	Counting oddball: No group difference on P2 or N2. Smaller P3b amplitude during rare trials in TS patients. Following CBT, there was a localized (left parietal cortex) P3b amplitude increase during rare trials. Motor oddball: No group difference on P2, N2, and P3b.
Morand-Beaulieu et al. (2018)	26	26	Stimulus-response compatibility paradigm	No group difference regarding accuracy or RT.	N2, P3b, LRP	No group difference on the N2. The No-Go P3b was larger over frontal electrodes in TS patients but did not differ in the other conditions. This study confirmed that previous findings regarding the treatment effects of motor-related components (Morand-Beaulieu et al., 2015) were not attributable to a practice effect. Finally, an electrophysiological model of treatment outcome prediction was found.
Oades et al. (1996)	10	12	Passive three-tone auditory oddball task	N/A	P1, N1, P2, N2, P3b, MMN	At electrode Cz, the P2 was larger and its latency was shorter in TS patients than HC. Also at electrode Cz, the N2 was delayed in TS patients. P1, N1, P3b and MMN did not differ between groups. The MNM was more posteriorly distributed in TS patients, while the usual posterior distribution of the P3b was less marked.

Obeso et al. (1981)	6	0	Spontaneous tics & voluntary imitation of tics	N/A	BP	No BP prior to tic onset was reported in any of the patients.
O'Connor et al. (2001)	12	14	Traffic light test	N.R.	MP	TS patients had larger MP amplitude than HC in the controlled condition, but smaller MP amplitude in the automated condition. TS patients had shorter MP onset latency (only during the 1st block) in the controlled condition.
O'Connor et al. (2005)	13	14	Traffic light test	No group difference regarding RT.	BP, MP	During automated trials, BP latency was faster in HC. In the second block of automated trials, HC had larger BP amplitude. TS patients had larger MP amplitude than HC in the controlled condition, but smaller MP amplitude in the automated condition. TS patients had shorter MP onset latency (only during the 1st block) in the controlled condition.
Petruo et al. (2018)	35	39	Visual-auditory Go/No-Go	In the No-Go condition without auditory stimuli, TS patients made more commission errors than healthy controls. There was no group difference regarding RT.	P1, N1, N2, P3b	There was no between-group difference regarding standard ERPs. However, through the residue iteration technique, it was found that TS patients had higher C-cluster amplitude in the N2 time window, during the No-Go condition without auditory stimuli. This higher amplitude could reflect some difficulties to withhold a response.
Rothenberger et al. (2000)	11	11	Auditory selective-attention task	TS+ADHD patients made more commission errors than HC	MMN, Nd', P3b	TS+ADHD patients tended to show lower MMN amplitude than HC but had normal Nd' and P3b.
Sauvé et al. (2017)	12	15	Visual oddball task with motor responses	No group difference regarding accuracy or RT.	P3b	Despite a general tendency toward reduced P3b amplitude in TS patients, there was no statistical difference between them and HC.
Schuller et al. (2018)	15	15	Stop-signal task	No group difference regarding accuracy or RT.	N2, P3b, ERN, Pe	During stop stimuli, TS patients showed attenuated P3b amplitude compared to healthy controls. TS patients also showed increased ERN but decrease Pe. There was no group difference regarding the N2.
Shephard et al. (2016a)	34[d]	20	Go/No-Go	TS patients had slower RT. There was no group difference regarding accuracy.	N2, P3b, ERN, Pe	The TS factor had no impact on any of the ERP measures. Patients with ADHD, and therefore TS+ADHD patients, had smaller N2, P3b, ERN, and Pe amplitude.
Shephard et al. (2016b)	35[e]	20	Reinforcement-basedlearning and reversal task	No group difference regarding accuracy or RT.	P2, P3b, FRN	Acquisition phase: no difference between groups. Reversal phase: Smaller P2 amplitudes in TS-ADHD patients when compared to HC and TS+ADHD patients. Trend toward smaller P3b amplitude in TS+ADHD patients when compared to HC and TS-ADHD patients. In TS+ADHD patients, those with the most severe ADHD symptoms had the largest FRN amplitude.
Siniatchkin and Kuppe (2011)	7	12	S1-S2 paradigm	N.R.	Early and late CNV	The amplitude of the total CNV was lower in TS patients, and it was negatively associated with tic severity.
Surwillo (1981)	1	5	S1-S2 paradigm	N.R.	P1, N1, P2, N2	The TS patients had shorter P2 and N2 latencies. The N1-P2 and P2-N2 amplitude differences were also smaller in the TS patient, suggesting a reduced P2. The differences disappeared following haloperidol treatment.
Tijssen et al. (1999)	3[f]	0	Spontaneous tics	N/A	BP	Patients did not show any premovement potential prior to tics.
Thibault et al. (2008)	26	14	Visual counting oddball	N.R.	P2, P3b	No group difference regarding the amplitude or latency of the P2, nor the latency of the P3b. Regarding the anterior P3b amplitude, TS-only patients did not differ from HC, but had larger anterior P3b amplitude than TS+OCD patients. TS-only also had larger posterior P3b amplitude than TS+OCD patients and HC.
Thibault et al. (2009)	15	20	Stimulus-response compatibility	No group difference regarding accuracy. Trend toward slower RT in TS patients.	NGA, P3b, LRP	General tendency toward a more frontally distributed NGA in TS patients. No group difference regarding the amplitude of the P3b. The P3b was delayed in TS patients during incompatible trials. The sLRP onset was delayed in TS patients, but there was no group difference regarding the rLRP.
van de Wetering et al. (1985)	6	16	Auditory oddball with motor responses	N.R.	N1, P2, N2, P3b	N1 to both standard and deviant stimuli were smaller in TS patients. The amplitude of the N1 increased following pharmacological treatment but remained smaller than in HC. At electrode Cz, the P3b to deviant stimuli was faster prior to pharmacological treatment in TS patients, but there was no difference following treatment. Also, the latencies of the parietal N2 and the frontal P2 to deviant stimuli were faster in TS patients

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Table 2 (*continued*)

Study	TS patients (n)	Healthy controls (n)	Experimental task/condition	Behavioral results	Components assessed	ERP results
						after treatment than in HC.
van der Salm et al. (2012)	14	25	Spontaneous jerks (motor tics) & intended self-paced wrist extension	N/A	BP	43% of TS patients had a BP prior to motor tics. 93% of TS patients and 100% of HC had a BP prior to wrist extension.
van Woerkom et al. (1988a)	20	20	Auditory passive oddball task & auditory oddball with motor responses	No difference between TS patients and HC regarding RT.	N1, P165, P2, MMN, N2b, P3b, SW	In the passive oddball task, TS patients showed smaller and faster P2 to standard stimuli, over central and parietal electrodes. There was no group difference regarding the MMN, P3b or SW, but the P165 and N2b were less discernible in TS patients. In the motor oddball task, the N1 to standard stimuli was smaller in TS patients. The deviant-standard difference N2b was also smaller at electrode Cz, but other components did not differ between groups.
van Woerkom et al. (1988b)	18	15	S1-S2 paradigm	No difference between TS patients and HC regarding RT.	Early and late CNV, PINV	At all electrode sites, TS patients showed a decreased early CNV and an increased PINV. There was no group difference regarding the late CNV.
van Woerkom et al. (1994)	53	41	Auditory passive oddball task & auditory oddball with motor responses	N.R.	N1, P2, N2, N400	In the passive oddball task, adults with TS had smaller amplitude in the P2-N2 time window at all electrode sites. Children with TS also had smaller N1 at electrodes C3 and P3, but larger N2 and N400 at electrode Fz. In the oddball task with motor responses, adults with TS had smaller N1 at all electrode sites, but no other group difference. Children with TS showed smaller N1 at Fz, and larger N2 at Fz and central electrodes.
Weate et al. (1993)	12	10	S1-S2 paradigm	N.R.	Early and late CNV, PINV	Despite non-significant results, TS patients tended to show reduced early CNV and increased late CNV. Reduced early CNV could be attributable to comorbid ADHD. PINV did not occur in HC but was seen in 7 TS patients.
Yordanova et al. (1996)	22	11	S1-S2 paradigm	TS+ADHD patients had slower RT.	Early and late CNV	TS patients had smaller early CNV amplitude and tended to show smaller late CNV amplitude.
Yordanova et al. (1997)	22	11	S1-S2 paradigm with 3 conditions (level of control)	No group difference regarding RT.	PINV	The was no group difference in the control condition. TS-only patients had larger PINV amplitude in the loss-of-control than in the lack-of-control condition, while TS+ADHD patients had larger PINV amplitude in the lack-of-control than in the loss-of-control condition.
Zhu et al. (2006)	34	20	Auditory oddball task with motor responses	N.R.	P3b	Globally, TS patients showed smaller P3b amplitude at all electrode sites, but shorter latency only at C4 site. The TS+ADHD subgroup had shorter P3b latencies than HC at all electrodes sites, and shorter latencies than TS-ADHD patients at Cz and Pz. TS-ADHD patients had smaller P3b amplitude than HC at all electrode sites, and smaller P3b amplitude than TS+ADHD at Cz. TS+ADHD patients had smaller P3b than HC only at Pz.

ADHD: attention deficit hyperactivity disorder, BP: bereitschaftspotential, CNV, Contingent negative variation, ERN: error-related negativity, FRN: feedback-related negativity, HC: healthy controls, MMN: mismatch negativity, MP: motor potential, N/A: not applicable, Nd: negative difference wave, NGA: No-Go Anteriorization, N.R.: not reported, NS': negative slope, OCD: obsessive-compulsive disorder, Pe: error positivity, PINV: postimperative negative variation, RT: reaction time, SRC: stimulus-response compatibility, SW: slow wave, TS: Tourette syndrome.

[a] Premovement potentials were only tested in one of the three patients.

[b] Children with TS were compared to children with transient tic disorder.

[c] This group included 6 TS patients, 1 chronic tic disorder patient, 1 transient tic disorder patient, and 1 tic disorder not otherwise specified patient. All nine patients had comorbid OCD.

[d] Behavioral analyses were performed on 34 TS patients (17 TS-ADHD & 17 TS+ADHD), but 2 TS-ADHD and 2 TS+ADHD patients were removed from ERP analyses.

[e] Behavioral analyses were performed on 35 TS patients (18 TS-ADHD & 17 TS+ADHD), but 1 TS-ADHD and 2 TS+ADHD were removed from ERP analyses.

[f] Premovement potentials were only tested in two of the three patients.

surement of the MMN quite difficult (Naatanen, 2000). While the generators of the P165 have not been studied extensively, multiple reports identified the frontal and temporal cortices as the principal sources of the MMN (Garrido et al., 2009). In auditory oddball tasks, adults with TS show similar MMN amplitude to that of healthy controls (van Woerkom et al., 1988a; Oades et al., 1996). In children with TS+ADHD, it was however slightly reduced, in comparison with healthy controls (Rothenberger et al., 2000). The related negative difference wave (Nd), which represents the difference wave of two auditory brain potentials, was nevertheless intact (Rothenberger et al., 2000). These results suggest that MMN is generally intact in TS patients, but that comorbid ADHD could induce an attenuation of this component. Reduced MMN has been clearly established in ADHD patients (Cheng et al., 2016).

Only one study reported P165 data in TS patients. In a passive auditory oddball task, the P165 was less discernible in TS patients than in healthy controls, while it did not differ in a motor oddball task (van Woerkom et al., 1988a).

3.2.4. N170

The N170 is a potential related to face processing (Rossion et al., 2008) and has generating sources in multiple brain areas such as the fusiform, lingual, and posterior inferior temporal gyri, as well as the superior temporal sulcus (Shibata et al., 2002; Itier et al., 2004). Our literature search only identified one study that assessed the N170 in TS patients. When presented angry faces cues, TS children presented shorter latencies of the N170 (Kalsi et al., 2018). Also, target-locked ERPs revealed larger fronto-central N170 amplitude for TS patients in the incongruent condition.

3.2.5. P2

The P2 is thought to reflect attentional processes such as the evaluation of stimulus salience and its task-related adequacy, and is partly generated by the orbitofrontal cortex (Potts et al., 2001; Potts et al., 2004). It is usually elicited during target detection tasks, such as the oddball task. Consequently, the P2 has mostly been elicited through oddball paradigms in TS patients. In children with TS, some oddball studies reported intact P2 latency (Drake et al., 1992) or amplitude (van Woerkom et al., 1994). Similarly, normal amplitude was found in a modified Eriksen-Flanker task (Eichele et al., 2016, Eichele et al., 2017).

Reduced amplitude of the P2 has been reported sparingly. In a single-case study, a 13 year-old TS patients showed a reduced P2 with shorter latency, during an auditory paired-stimuli task (Surwillo, 1981). And in a reinforcement-based learning and reversal task, TS children without ADHD had smaller feedback-locked P2, in comparison to TS+ADHD children and healthy controls (Shephard et al., 2016b). In presence of an intact behavioral performance, the authors argued that this effect could be induced by less reliance on feedback than healthy controls. This suggests that TS children without ADHD have better reversal learning abilities than the latter group and TS+ADHD children.

Larger P2 amplitude and reduced latency have also been found in children with TS (Oades et al., 1996). This appears to be the only case where P2 amplitude was larger in TS patients, which could be caused by significant ADHD symptoms within this group. Indeed, enhanced P2 has been previously reported in children with ADHD (Lazzaro et al., 2001; Senderecka et al., 2012). Similarly to its association with ADHD symptoms, P2 amplitude has been positively associated with tic severity in children (Eichele et al., 2017). Therefore, the reduced P2 reported in some studies could indicate some sort of mechanism to gain control over tics.

In adults with TS, most studies using oddball tasks revealed no difference between TS patients and healthy controls regarding P2 amplitude (van de Wetering et al., 1985; Thibault et al., 2008; Morand-Beaulieu et al., 2016) or latency (van de Wetering et al., 1985; Thibault et al., 2008). However, two studies from the same lab reported faster and reduced P2 in TS adults, only during frequent trials in a passive oddball task, while this component was intact during the motor condition (van Woerkom et al., 1988a; van Woerkom et al., 1994). Therefore, P2 alterations are not so frequent among TS patients, but a reduced amplitude seems possible. Future studies should always consider the effect of medication on the P2, since it has been proved to accelerate its latency (van de Wetering et al., 1985).

3.2.6. N2

The N2 is traditionally seen as an index of cognitive control, a term that encompasses response inhibition as well as conflict and response monitoring (Folstein et al., 2008). It can be elicited through multiple paradigms, such as oddball, flanker, Go/No-Go, or Simon tasks, among others. An important generator of the N2 is the anterior cingulate cortex (Folstein et al., 2008). Only few studies assessed the N2 in TS children. Among them, both intact (Drake et al., 1992) and delayed N2 latency (Oades et al., 1996), as well as intact (Oades et al., 1996; Shephard et al., 2016a; Petruo et al., 2018) and enhanced N2 amplitude (van Woerkom et al., 1994) were reported. Comorbid ADHD could explain some discrepancies regarding N2 latencies, since TS+ADHD patients were shown to have delayed N2 latency (Drake et al., 1992), and children in the study of Oades et al. (1996) had high scores on the Conner's ADHD scale. Similarly, the ADHD factor, but not the TS factor, had been associated with slightly reduced N2, suggesting a possible reduction of that component in TS+ADHD patients (Shephard et al., 2016a). In his single-case study, Surwillo (1981) found shorter latency and smaller amplitude of the N2 in a 13 years-old TS patient. Haloperidol treatment made the N2 latency and amplitude more like that of the control group. While it is not stated if this patient had comorbid ADHD or not, we may think that his severe tics could lead to a certain number of attentional deficits.

In adults, many discrepant findings have been reported as well. In motor oddball tasks, few studies found no difference in N2 amplitude between TS patients and healthy controls (van de Wetering et al., 1985; van Woerkom et al., 1994; Morand-Beaulieu et al., 2016). Yet, enhanced (Johannes et al., 1997) and reduced (van Woerkom et al., 1988a) N2 amplitude have also been reported.

Researchers have also used oddball tasks that do not require a motor response to elicit the N2 in TS patients. Intact N2 was reported in a counting oddball task (Morand-Beaulieu et al., 2016), but a larger N2 was found in a passive oddball task, where no action was required from patients (van Woerkom et al., 1994). Few other paradigms revealed a larger N2 in TS patients, such as a pop-out experiment (Johannes et al., 1997) or a Stop paradigm (Johannes et al., 2001a). However, the Stroop task (Johannes et al., 2003), the stimulus-response compatibility paradigm (Morand-Beaulieu et al., 2018), the stop-signal task (Schuller et al., 2018), and the figure extraction and conjunction paradigms (Johannes et al., 1997) did not reveal any N2 difference between TS patients and healthy controls.

Therefore, N2 impairments in TS patients could be task-dependent. In adults with TS, van Woerkom et al. (1994) suggested that over attention to standard stimuli in a passive oddball task results in an extensive attentional processing that creates a larger negative activity in the 200–300 ms interval. The superimposition of this activity on the N1-P2 complex could account for the diminished amplitude in the 200–300 ms interval. In an active oddball paradigm, where attention to target stimuli is more important, the group difference in this interval disappeared. In children, differences were mostly seen during the active condition. Indeed, these patients had larger N2 and N400 components, reflecting possible extra processing of standard stimuli. Also, as reported by Petruo et al. (2018), the overlap between stimulus and response processing

in the N2 time window could hinder the detection of certain group differences. Using the residue iteration decomposition (RIDE) technique, they found significant group differences in the N2 time window during the unimodal No-Go condition, where TS patients had larger C-cluster amplitude than healthy controls. The latter would reflect, according to the authors, more difficulties in withholding a motor response (Petruo et al., 2018).

3.2.7. P3

The P3 is usually separated into two subcomponents: the P3a and the P3b. The P3a was first observed in a three-stimulus oddball task, where an infrequent non-target stimulus would elicit a positive deflection over frontal and central electrodes. This potential is thought to reflect early attentional processes, such as orienting or shifting the focus of attention to new or unexpected stimuli (Polich, 2007). The other subcomponent of the P3 family, the P3b, is typically larger over parietal electrodes. In a typical oddball task, its amplitude is larger for target than standard stimuli. Many factors may influence P3b amplitude or latency, but it is thought to reflect stimulus evaluation and context updating in working memory (Donchin et al., 1988). Current evidence suggests that the P3a and P3b are generated from sources located in the frontal and temporal/-parietal areas (Polich, 2007). Often, when articles report P3 data, they are mostly referring to the P3b (Luck, 2005). We therefore assumed it was the case when no specification was given about the nature of the P3, if its latency, its cortical distribution, and the task used to elicit the component were coherent with the P3b.

3.2.7.1. P3a. Very few studies assessed the P3a in TS patients. In an emotional Simon task, TS children had larger P3a amplitude (called LC1) to incongruent trials (Kalsi et al., 2018). In a modified Eriksen-Flanker task, TS children showed larger P3a, in comparison to ADHD and healthy controls (Eichele et al., 2016). However, that difference was no longer significant when children were reassessed almost five years later (Eichele et al., 2017).

3.2.7.2. P3b and late positive potentials. Not surprisingly, the P3b was the most studied component in TS patients. There are several discrepancies across studies, and some inconsistency can be attributed to the different paradigms that have been used to elicit the P3b. In children with TS, intact P3b amplitude has been reported during a modified Eriksen-Flanker task (Eichele et al., 2016; Eichele et al., 2017), an auditory selective-attention task (Rothenberger et al., 2000), and a Go/No-Go paradigm (Petruo et al., 2018). In an auditory oddball task, Oades et al. (1996) did not report significant P3b impairments in TS patients, but its parietal distribution was less marked. Yet, some studies using oddball tasks reported smaller P3b (Chen et al., 1997; Zhu et al., 2006). Comorbid ADHD could be a confounding factor, since TS patients tend to show P3b decrements in Go/No-Go (Shephard et al., 2016a) and reinforcement-based learning and reversal (Shephard et al., 2016b) tasks when ADHD symptoms reach a clinical threshold. However, in the study of Zhu et al. (2006), a subgroup of TS-ADHD patients showed smaller P3b amplitude than healthy controls at all electrode sites, while this was only true at electrode Pz for the TS+ADHD subgroup. And surprisingly, TS+ADHD patients had larger P3b amplitude than TS-ADHD patients at electrode Cz. Another study reported that nicotine treatment allowed TS children's P3b amplitude to remain stable over a two-week interval, while it decreased in a placebo condition (Howson et al., 2004). The LC2, which is similar to the P3b, was shown to be increased during the presentation of incongruent stimuli in an emotional Simon task (Kalsi et al., 2018). Moreover, LC2 amplitude related to the presentation of incongruent targets after anger cues was positively associated to tic severity.

Globally, P3b latency does not appear to be extensively affected in TS children without comorbidities (Zhu et al., 2006). Yet, faster P3b latency has been reported in TS children with comorbid OCD (Drake et al., 1992) or ADHD (Zhu et al., 2006). In a group of TS children with high Conner's ADHD scale scores, Oades et al. (1996) also reported shorter posterior P3b latency in comparison with anterior sites

In adults, intact P3b amplitude was found in pop-out experiment and figure extraction paradigm (Johannes et al., 1997), oddball task (van de Wetering et al., 1985; van Woerkom et al., 1988a; Johannes et al., 2001a; Johannes et al., 2002), Stroop paradigm (Johannes et al., 2003), Simon task (Thibault et al., 2009; Morand-Beaulieu et al., 2015, Morand-Beaulieu et al., 2018). However, some studies reported smaller P3b amplitude during oddball (Johannes et al., 1997, Morand-Beaulieu et al., 2016) and dual-task paradigm (Johannes et al., 2001b). And while the group difference did not reach statistical significance, Sauvé et al. (2017) reported a general tendency toward a reduced P3b in non-medicated and non-comorbid adults with TS during an oddball task. This could be caused by a lack of power, given the relatively small sample size in that study. Furthermore, CBT induced an increase in oddball-P3b amplitude, which was localized over the parietal cortex (Morand-Beaulieu et al., 2016). In a stop-change task, the P3b was smaller in immediate change trials in adults with TS, which is hypothesized to represent a better multi-sensory integration during response selection processes (Brandt et al., 2017). While most studies reported intact or diminished P3b amplitude, Lange et al. (2017) found a larger cue-locked parietal P3b amplitude during a computerized Wisconsin Card Sorting Task. This discrepancy with other studies could be explained by the task used in their study. While most tasks eliciting a P3b consisted of stimulus detection and/or categorization, this task involved cognitive flexibility. Since cue-locked P3b is associated to proactive cognitive control processes, this enhanced component in TS patients suggest an additional recruitment of cognitive resources to ensure efficient cognitive flexibility. Surprisingly, Thibault et al. (2008) reported larger parietal P3b amplitude in TS patients, compared to healthy controls. Here, the control group seems odd when compared to other studies. While TS patients had similar P3b parietal amplitude to those of a recent study (Morand-Beaulieu et al., 2016), healthy controls' amplitude was more than twice as small. Healthy controls aside, this study yields interesting findings regarding the contribution of comorbid OCD on electrophysiological markers of TS. Indeed, TS+OCD patients had lower P3b amplitude than TS-only patients.

Regarding the latency, the P3b was found to be delayed in response to incompatible stimuli in a Simon task (Thibault et al., 2009), and during a figure conjunction paradigm (Johannes et al., 1997). Yet, other studies reported intact P3b latencies, in oddball tasks (van Woerkom et al., 1988a; Johannes et al., 2001a; Johannes et al., 2002; Thibault et al., 2008), Stroop paradigm (Johannes et al., 2003). Faster latency of the P3b was reported in six TS patients during an oddball task (van de Wetering et al., 1985). Yet, their P3b latency was no longer different from healthy controls following pharmacological treatment.

Some studies also studied the anteriorization effect of the P3b on No-Go or stop trials. In healthy controls, the No-Go P3b (or No-Go Anteriorization; NGA) is generally distributed over central electrodes (Fallgatter and Strik, 1999), in comparison with the posterior distribution of the P3b. However, in TS patients, many studies reported a frontal shift of this component (Johannes et al., 2001b; Thibault et al., 2009, Morand-Beaulieu et al., 2015; Morand-Beaulieu et al., 2018). Yet, in a recent study, Schuller et al. (2018) found the same topographical distribution of the P3b related to stop stimuli, and reported that this component was reduced in TS patients. Such differences might be explained by different processes required to stop an already ongoing response (stop-signal task) and to inhibit a response in its early stages of activation (Go/No-Go task) (Johnstone et al., 2007).

3.2.8. N400

The N400 is typically related to semantic processing and recognition memory (Kutas and Federmeier, 2011). While this component appears to be generated by a network of sources distributed throughout the brain, the left temporal lobe is probably the principal generator of the N400 (Van Petten and Luka 2006; Kutas and Federmeier, 2011). In word recognition tasks, the N400 reflects the integration of the attributes of the presented item with its prior context (Dietrich et al., 2001). In an emotional word recognition paradigm, TS patients showed reduced N400 old-new effect for negative and positive words, but did not differ from healthy controls for neutral words (Johannes, 1999). This suggests a different processing of emotional words among TS patients. The N400 is also elicited by incongruent stimuli in a Stroop paradigm (Rebai et al., 1997). Johannes et al. (2003) reported larger and delayed N400 (designated as N450 in their article) in TS patients, suggesting enhanced and prolonged neural activity to process incongruent trials. Another study reported N400 data in TS patients, however it was not related to the processing of words. In a passive oddball task, van Woerkom et al. (1994) found that children with TS showed larger negativity over the frontal cortex around 400 ms post-stimulus. The authors argued that this component reflected extra processing of frequent stimuli in those patients.

3.2.9. Error-related potentials

Error-related potentials can be elicited through a wide range of behavioral tasks, as long as participants make a sufficient number of errors (at least six trials in a block (Pontifex et al., 2010)). These potentials are time-locked to the response rather than the stimulus. Following an error, we typically see a negative deflection over frontal and central electrodes. This potential is called the error-related negativity (ERN). It is often followed by a positive component: the error positivity (Pe) (Luck, 2005). Generating sources of these potentials were mostly found in the anterior cingulate cortex (Van Veen and Carter (2002); Wessel, 2012). In a modified Eriksen-Flanker task, Eichele et al. (2016) reported no difference between children with TS and healthy controls regarding ERN, which was absent in most cases. In a follow-up study conducted almost five years later, they reported an increase in ERN amplitude, which was also observed in healthy controls (Eichele et al., 2017). The increase in ERN amplitude was larger in TS children and healthy controls than in children with ADHD. The ERN was also negatively correlated with tics severity, suggesting a functional adaptation of the medial frontal cortex in order to control tics. Similarly, Shephard et al. (2016a) reported similar ERN in children with TS and healthy controls, but reduced amplitude in children with both TS and ADHD. In a similar task, children with various tic disorders and OCD did not differ from healthy controls regarding ERN amplitude, while it was larger in children with solely OCD (Hanna et al., 2012). In adults with TS, larger ERN amplitude has been found in TS patients (Johannes et al., 2002). Yet, 60% of the TS sample in the study had moderate or severe OCD symptoms. A recent study where no patient had comorbid OCD also revealed increased ERN (Schuller et al., 2018), suggesting that this feature is not entirely attributable to OCD symptomatology.

The feedback-related negativity (FRN), which is similar to the ERN but usually time-locked to a feedback stimulus, appears to be linked to ADHD symptoms in TS patients. Shephard et al. (2016b) reported that TS+ADHD patients with most severe symptoms showed the largest FRN, suggesting over-reliance on external feedback to produce the correct response. This link between symptoms intensity and error-related negativity is also consistent with the results of Eichele et al. (2017).

Positive post-error components, such as the early positivity and the error positivity (Pe), appear to be intact in children with solely TS (Eichele et al., 2016; Shephard et al., 2016a; Eichele et al., 2017). Yet, reduced Pe was found in children with TS+ADHD (Shephard et al., 2016a) and in adults (Schuller et al., 2018).

3.2.10. Slow cortical potentials

A few early ERP studies of TS have focused on preparatory potentials that are elicited by paired-stimuli (S1-S2) paradigms. These paradigms imply the presentation of two stimulus: a warning stimulus and an imperative stimulus, after which a response must be given (Kropp et al., 2000). One of these potentials is the contingent negative variation (CNV), which is generally composed of two waves: the early and the late CNV. The early CNV follows the presentation of the warning stimulus (S1), whereas the late CNV precedes the imperative stimulus (S2) (Kropp et al., 2000). The early CNV represents an orientation response, while the late CNV is linked to expectancy and response preparation (Taylor et al., 2016). These potentials have generators located in the primary and supplementary motor areas, the premotor area, the primary sensory area, and the prefrontal, parietal, and occipital cortices (Hultin et al., 1996; Hamano et al., 1997). The early CNV appears to be reduced in TS patients. In children, all studies indicated a reduced or a tendency toward a reduced early CNV (Dumais-Huber and Rothenberger, 1992; Siniatchkin and Kuppe, 2011). A similar trend was observed in adults with TS, as van Woerkom et al. (1988b) found a reduced early CNV and Weate et al. (1993) reported a decrease of the same component, which was however statistically non-significant. Results are somewhat less clear regarding the late CNV. In children, the early study of Dumais-Huber and Rothenberger, 1992 suggested an intact late CNV, but later reports found a trend toward a reduction of that component (Yordanova et al., 1996; Siniatchkin and Kuppe, 2011). In adults, both an intact (van Woerkom et al., 1988b) and a non-significantly increased (Weate et al., 1993) late CNV were reported.

The postimperative negative variation, as its name indicates, is a negative potential that follows the imperative stimulus. The PINV is seen as a prolongation of the CNV beyond the imperative stimulus in S1-S2 paradigms (Kathmann et al., 1990; Kropp et al., 2000). It is associated to the processing of contingency changes and the handling of lack of control over aversive stimuli (Kathmann et al., 1990). In children with TS, it was shown to be intact in typical S1-S2 paradigms (Dumais-Huber and Rothenberger, 1992; Yordanova et al., 1997). However, differences appeared in a more complex version of this paradigm, where patients do not control the duration of an aversive S2 stimulus. In this paradigm, TS-only patients had larger PINV amplitude in the loss-of-control than in the lack-of-control condition, while TS+ADHD patients showed the opposite (Yordanova et al., 1997). Their results indicated that the effects on TD and ADHD were interdependent and not additive at the psychophysiological level. In their study, children with TS+ADHD had a similar profile to that of healthy controls regarding the PINV amplitude, while TS-only children had larger PINV amplitude in the loss-of-control condition. Only few studies reported PINV data in adults with TS. In their study, Weate et al. (1993) failed to identify a PINV in any of their control participant, but it could be identified in more than half of TS patients. However, they did not report amplitude data. Another study found an increased PINV in TD patients, which was significant at all electrode sites, except for the right parietal region (van Woerkom et al., 1988b).

3.2.11. Motor-related potentials

Motor-related potentials, such as the *Bereitschaftspotential* (BP) or the lateralized readiness potential (LRP), are highly relevant to the study of TS, given the motor aspect of its main symptoms. These potentials typically precede voluntary movements and have generators in the primary (Miller and Hackley, 1992; Requin and

Riehle, 1995; Praamstra et al., 1999) and supplementary motor areas (Rektor, 2002). Some studies tested the presence of a premovement potential prior to tic onset, and it was reported that this potential was mostly absent (Obeso et al., 1981; Tijssen et al., 1999; Bour et al., 2015). Yet, these studies included very few patients. An investigation on three TS patients reported a BP before tics in all of them (Duggal and Nizamie, 2002) whereas two other studies showed that a BP prior to tic onset was present in approximately 40% of the patients (Karp et al., 1996; van der Salm et al., 2012). The study of Karp et al. (1996) also revealed that the negative slope (NS') obtained during spontaneous tics was similar to the NS' obtained during voluntary movements. This suggests a volitional aspect of tics in an important proportion of patients. Since the BP onset observed by Duggal and Nizamie (2002) was shorter than in typical movements by healthy controls, the term "quasi-volitional" might be more appropriate. Some research remains to be done to understand why some patients present such cerebral potential before tics and some do not. This potential could also be linked to premonitory urges.

Other studies assessing premotor potentials did so using specifically tailored experimental tasks. One of these tasks is the traffic light test, which is essentially a S1-S2 paradigm. In this paradigm, the warning stimulus announces the type of response to give, either an automated (three taps on a key: – – –) or a controlled response (three taps of Morse code: – –). Then, the imperative stimulus indicates when to respond. A stop stimulus could also appear, indicating that the response must be terminated. During automated trials, TS patients showed delayed BP latency and reduced BP amplitude (only in second block of trials (O'Connor et al., 2005)).

In TS patients, the motor potential (MP) was larger for controlled than automated trials, while healthy controls showed the opposite (O'Connor et al., 2001; O'Connor et al., 2005). And in the 1st block of controlled trials, TS patients had shorter MP onset latency than healthy controls (O'Connor et al., 2001; O'Connor et al., 2005). Amplitude of the MP has been positively correlated to tics symptoms (Lavoie et al., 2011). Furthermore, Lavoie et al. (2011) also reported that the go-stop amplitude difference in automated trials was smaller in TS patients, in comparison with healthy controls. This effect however normalized after CBT.

Only few studies investigated LRPs in TS patients, and important discrepancies were reported. Johannes et al. (2001a) were the first to assess the LRP in TS patients and did not report any group difference. However, this LRP was only elicited by a go stimulus, and that paradigm could have lacked the specificity to detect impairments in motor processing in TS patients. Using a stimulus-response compatibility paradigm, Thibault et al. (2009) found that TS patients had faster incompatible sLRP onset than healthy controls. However, our research group evaluated the sLRP onset in a group of TS patients and compared it with two different sets of healthy controls (Morand-Beaulieu et al., 2015; Morand-Beaulieu et al., 2018). In both studies, we found merely the opposite: slower sLRP in TS patients. This discrepancy can be explained by the delayed responses of the healthy controls in the study of Thibault et al. (2009). In our recent studies, the TS patients' sLRP onset latency was similar to those included in the study of Thibault et al. (2009), while the sLRP onset of healthy controls was much faster. The incompatible sLRP onset was also part, with the incompatible N2, of a model that predicted CBT outcome in TS patients (Morand-Beaulieu et al., 2018). Motor potentials associated to the execution of the motor responses were also studied in TS patients. While Thibault et al. (2009) did not found any between-group difference regarding LRP amplitude, our research group recently reported larger rLRP peak in TS patients, which normalized following CBT (Morand-Beaulieu et al., 2018).

4. Discussion

The main goal of the current review was to expose the state of the science regarding cognitive and motor-related ERPs in TS patients. Some components have been studied in only a few occurrences, making it hard to draw clear conclusions. All in all, it appears clear that the early CNV is reduced in both children and adults with TS. Also, there seems to be constant differences between healthy controls and TS patients regarding motor-related potentials, which are consistent with impairments in fine motor skills found in TS (Abramovitch et al., 2017). Other components, such as the N2 or the P3b, were studied frequently, but many discrepancies exist between studies. It seems possible that the P3b could be slightly reduced in TS patients, during tasks involving stimulus detection and attention, as some studies found reduced P3b in oddball tasks (Chen et al., 1997; Johannes et al., 1997; Zhu et al., 2006; Morand-Beaulieu et al., 2016). It is possible that the decrements are so light that most studies lack the necessary power to detect such effect. Future studies should try to highlight the factors influencing P3b amplitude in TS patients. Discrepancies between studies might also be caused by the different paradigms used in these studies, or by the inclusion of patients with comorbid disorders or with various level of symptoms' severity.

4.1. Impact of comorbidity

While some electrophysiological particularities appear to be intrinsic to TS, a lot of the differences between healthy controls and TS patients can be attributed to comorbid ADHD. This common comorbidity of TS is known to be a confounding factor in patients' cognitive abilities (Sukhodolsky et al., 2010; Morand-Beaulieu et al., 2017a). One must truly appreciate the effort made by Shephard et al. (2016b, a) to understand the contribution of ADHD to the ERP of TS patients. Their studies, which used a 2×2 design with TS and ADHD factors, revealed that most impairments were focused to TS+ADHD children, while those without ADHD showed little difference with healthy controls. For instance, P3b decrements were focused toward children affected by ADHD. Surprisingly, Zhu et al. (2006) found the opposite, with TS+ADHD patients showing larger P3b (at electrode Cz) than patients without comorbid ADHD. However, they reported that more than half of their TS+ADHD sample showed irregular P3b waveforms, which could explain this divergent finding. Also, many TS studies reported N2 particularities, either a reduced amplitude or a delayed latency, that were attributable to comorbid ADHD (Drake et al., 1992; Oades et al., 1996; Shephard et al., 2016a). Comorbid ADHD could also increase the P2 amplitude of TS patients (Oades et al., 1996; Shephard et al., 2016b), which was found to be reduced in TS-only children (Shephard et al., 2016b). The MMN was not extensively assessed among TS patients, but the only study that reported decreased MMN solely included patients with comorbid ADHD (Rothenberger et al., 2000).

Comorbid OCD, which was less studied than ADHD, might also have an impact on TS patients' ERP. In a direct comparison between TS-only and TS+OCD patients, the oddball P3b amplitude was shown to be diminished in the latter group (Thibault et al., 2008). In the same vein, Johannes et al. (1997) reported a decreased oddball P3b in a group of 12 TS patients, all of whom had comorbid OCD.

However, diminished P3b was also reported in TS patients with low levels of comorbidity (Morand-Beaulieu et al., 2016), and Sauvé et al. (2017) reported a general trend toward reduced P3b in non-medicated and non-comorbid TS patients. Particularities in motor-related potentials appear to be inherent to TS and

independent of comorbid disorders (Lavoie et al., 2011; Morand-Beaulieu et al., 2015), but it seems plausible that they could be potentiated by comorbid ADHD. Therefore, while some ERP particularities reported in the current review are caused by comorbid disorders, some impairments are truly attributable to TS.

4.2. Age differences

Based on the studies reported in the current review, it is hard to discern potential differences in TS patients' ERP based on their age. However, the studies of Eichel et al. (2016, 2017) are of great interest, since they performed two assessments almost five years apart. For instance, they reported that the ERN followed a normal developmental curve in children with TS. However, the P3a developed earlier in children with TS than in healthy controls. When reassessed in adolescence, the developmental trajectory of healthy controls' P3a converged with that of TS patients. This suggests that children with TS implement early adaptive strategies regarding attention orienting and stimulus evaluation (Eichele et al., 2017).

4.3. How are ERP components affected by treatment?

Very few studies aimed to understand the link between ERP and pharmacological treatments for TS symptoms, but some interesting findings were reported. In his case study, Surwillo (1981) reported that his patient's N2 and P2 latency and amplitude were normalized following haloperidol treatment. Pharmacological treatment (haloperidol or clonidine) also allowed to increase the amplitude of a diminished N1 in TD patients, which however remained smaller than in healthy controls (van de Wetering et al., 1985). It also allowed to normalize an accelerated P3b, but the latencies of the parietal N2 and the frontal P2 to target stimuli became faster after treatment than in healthy controls. Finally, nicotine treatment appears to counter P3b decrements in TS patients (Howson et al., 2004).

The impact of CBT on TS patients' ERP was not extensively studied either. The first study to assess this feature was conducted by Lavoie et al. (2011). Their study reported that a CBT allowed a normalization of the motor potential during a task involving the inhibition of automatic motor responses. Recent papers from our research group also investigated the impact of a CBT on other components. First, we reported a normalization of ERP components related to motor preparation and execution, namely the sLRP onset and the rLRP peak amplitude (Morand-Beaulieu et al., 2015, 2018). We also found a reduced P3b amplitude during a visual counting oddball task in TS patients (Morand-Beaulieu et al., 2016). The CBT allowed a parietally-localized normalization of this component to the level of healthy controls.

5. Limitations

This review has some limitations. It is hard to draw clear conclusions on some ERP components, given that some have rarely been assessed in TS patients, and because of the wide variety of paradigms used to elicit ERP. The impact of comorbidity is also hard to assess, since that only few studies performed direct comparisons between TS-only and comorbid patients. Another limitation of this review is that we cannot control for various levels of medication intake in individual studies. Studies evaluating the impact of medication on TS patients' ERPs are scarce, making it hard to draw clear conclusions regarding the impact of medication. Since some studies found ERP differences between non-medicated TS patients and healthy controls (e.g. O'Connor et al., 2005; Zhu et al., 2006; Kalsi et al., 2018), medication cannot be the sole cause for the differences that were reported in this systematic review. Another limitation is that sample sizes of included studies are sometimes small, which could give rise to discrepant findings across studies. Finally, there are limitations inherent to the systematic review procedure. We only included articles that were published in peer-reviewed journals. As we know, negative results are less likely to be published. Therefore, we cannot rule out a possible publication bias. Also, despite our thorough search in four databases and in the reference lists of included studies, it is possible that we have not retrieve all studies fulfilling our criteria. And although we aimed to be as objective as possible in our reporting of ERP findings, we cannot fully exclude the possibility of a reporting bias.

6. Future directions

In recent years, there has been a renewed interest toward ERP research in the field of TS, as 30% of studies included in this review were published after 2010. Generally, these studies have more sound methodology than older studies, and include larger samples of TS patients. We encourage further replication of findings reported in this systematic review, with large samples and good control of comorbidity. Studies comparing TS patients to other clinical groups that share some characteristics (e.g. ADHD, OCD, body-focused repetitive behaviors) are also welcome. We chose to focus this review on ERPs to remain as concise as possible. However, other EEG techniques are becoming more and more used in the study of TS patients. We warmly invite other TS researchers to perform systematic reviews of studies involving resting-state EEG or functional and effective connectivity, for instance.

The P3b was the most studied component, and available evidence points toward a possible reduction during oddball task. Given that differences between TS patients and healthy controls regarding this component seem small, future studies should focus on the determinants of ERP components, among large sample of TS patients. Such investigation would allow a thorough characterization of the factors contributing to TS patients' ERP particularities, whether it is tic severity, level of attentional impairment, or psychiatric medication intake, for instance.

7. Conclusion

All in all, ERP appears to be a useful technique to assess the neural underpinnings of motor and cognitive functioning in TS patients. Yet, since the severity of cognitive deficits in TS is generally mild, many studies might have lacked the statistical power to detect small to moderate effects between groups. Some discrepancies across studies could also be attributed to an inadequate control of comorbid conditions. In some domains that are usually more impaired among TS patients, such as motor functions or inhibitory control, ERP differences between healthy controls and TS patients are more constant.

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Conflict of interest

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