Lateral parietal cortex in the generation of behavior
Tumati, S; Martens, S; de Jong, B M; Aleman, A

Published in:
Progress in Neurobiology

DOI:
10.1016/j.pneurobio.2018.12.003

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 14-12-2019
Lateral parietal cortex in the generation of behavior: Implications for apathy

S. Tumati, S. Martens, B.M. de Jong, A. Aleman

Department of Psychology, University of Groningen, the Netherlands
Department of Neurology, University of Groningen, University Medical Center Groningen, the Netherlands
Mind, Brain Imaging and Neuroethics Research Unit, Institute of Mental Health Research, University of Ottawa, Royal Ottawa Mental Health Centre, Ottawa, ON, Canada
Department of Neurology, University of Groningen, University Medical Center Groningen, the Netherlands
Department of Psychology, University of Groningen, the Netherlands

ARTICLE INFO

Keywords:
Apathy
Parietal lobe
Inferior parietal lobule
Action initiation
Goal-directed behavior

ABSTRACT

A reduction in goal-directed behavior, or apathy, occurs in neurological and psychiatric disorders, though its neural substrates remain unclear. Deficits in circuits connecting the prefrontal cortex to subcortical regions are considered to underlie apathy. Although apathy is empirically associated with widespread changes in these regions, studies across disorders also link apathy with the lateral parietal cortex. Such variety in regional involvement is consistent with the established role of prefrontal and subcortical regions in models of goal-directed behavior, and with the suggestion of subtypes of apathy. However, these models do not provide a basis for the involvement of the lateral parietal cortex with apathy. Here, we review the association between lateral parietal cortex dysfunction and apathy across disorders and analyze the putative cognitive functions that may link this region with goal-directed behavior. We suggest that neural processes in the angular and supramarginal gyri of the inferior parietal lobule may provide an interface enabling the transformation of internal goals to external actions through intentional initiation of action interrelated with mechanisms of primary sensorimotor transformation. Consequently, we propose that impairment in this process of embedding intended action in a ‘body schema’ facilitating adequate recruitment of an effector system, is the likely mechanism underlying the association between the lateral parietal cortex and apathy. Considering the evidence, we propose a revised neurocognitive model of apathy where deficient internal initiation of behavior mediated by the inferior parietal lobule may be sufficient, though not necessary, to reduce goal-directed behavior, and may constitute a volitional subtype of apathy.

1. Introduction

Performing complex behaviors is part and parcel of daily life. For example, getting from A to B in a city requires the dynamic interplay of several cognitive processes, ranging from long-term memory and attention to planning abilities and spatial navigation. Thus, to successfully accomplish such behaviors, a variety of cognitive functions that rely on multiple brain regions must work together in an integrated manner. Cognitive models that describe the generation of such complex behavior comprise of cognitive functions that begin with an internally or externally driven motivation to act, followed by planning, executing actions, evaluating outcomes with respect to selected goals, and if required, adapting subsequent actions (Brown and Pluck, 2000). Deficits in any cognitive function forming this sequence of processes may lead to impairments in the generation of complex behaviors. Such reduced behavior, which is clinically termed as apathy (Levy and Dubois, 2006; Robert et al., 2009), is observed across various neurological and psychiatric disorders. It is characterized by several observable symptoms, such as lack of initiative, loss of interest, or lack of effort in performing day to day tasks.

The neural substrates of apathy have been suggested to lie in circuits linking the prefrontal cortex to subcortical structures (Bonelli and Cummings, 2007; Brown and Pluck, 2000; Levy and Dubois, 2006; Marin, 1990; Starkstein, 2000; Stuss et al., 2000; van Reekum et al., 2010). Indeed, studies in various disorders have implicated the dopaminergic system (Czernicki et al., 2008; Tanaka et al., 2003; Thobois et al., 2010), cholinergic system (Drijgers et al., 2009), and noradrenergic system (Barnhart et al., 2004) in apathy. The circuits linking...
these systems particularly to the striatum and prefrontal cortex are considered to be the basis of disorders of motivation. These disorders include severe behavioral impairment seen in akinetic mutism where patients are unresponsive to external commands, lack motor initiative, and are indifferent to internal states of pain or thirst (Mega and Cohen, 1997). This condition as well as a similar but less severe condition, termed abulia, are closely associated with lesions in the anterior cingulate cortex, ventral or limbic striatum (consisting of the ventral caudate, ventral putamen, nucleus accumbens, and olfactory tubercle), the ventral global pallidus, and medial thalamus (Mega and Cohen, 1997). On the basis of these studies, cortico-subcortical loops from the anterior cingulate cortex to the thalamus and striatum, and brainstem nuclei have been proposed to underlie motivational disorders in general (Bonelli and Cummings, 2007). The emphasis on frontostriatal circuits is easy to understand, as it is not only by inference of well-described functions attributed to these circuits that correspond with deficits expressed in apathy (Hazy et al., 2007; Miller and Cohen, 2001), but there is also empirical evidence for their association in apathy (Kos et al., 2016; McIntosh et al., 2015; Pagonabarraga et al., 2015; Stella et al., 2014; Theleritis et al., 2014).

Severe motivational disorders typically result from lesions due to tumors or vascular conditions. In comparison, apathy is a relatively less severe condition and develops in neurodegenerative conditions, typically over a long period (Aalten et al., 2007; Marin, 1990). However, apathy in these conditions is comorbid with other neuropsychiatric syndromes. In particular, symptoms of depression are often confused with those of apathy but have been found to have different neural substrates (Hollocks et al., 2015; Kirsch-Darrow et al., 2006; Levy et al., 1998; Starkstein et al., 2009).

Apathy in neurodegenerative conditions also shows subtypes, which are linked to deficits in specific prefrontal-subcortical loops that correspond with specific functional deficits (Levy and Dubois, 2006). Moreover, the associated neuropsychological deficits have been interpreted within a cognitive framework of goal-directed behavior (Brown and Plack, 2000). The components of goal-directed behavior include storage and evaluation of stimulus information, evaluation of reward potential of specific actions, and generation of a plan of action (Hollerman et al., 2000). The neural correlates of these components lie in the medial and lateral prefrontal cortex. The basal ganglia, which by means of extensive dopaminergic circuitry, signals reward potential and acts as a final gateway in the production of motor movements (Goto and Grace, 2005). In short, these circuits appear to support cognitive functions necessary for goal-directed behavior. Based on these observations, neurocognitive models of apathy consisting of subtypes with specific circuits and functional deficits have been proposed.

A critical reading of recent studies in different brain disorders, however, suggests that besides associations with the prefrontal cortex–basal ganglia regions, apathy is also associated with changes in the lateral parietal cortex (Fig. 1). This association, reported in diverse disorders, is of interest as the lateral parietal cortex does not find a place in current models of apathy (Bonelli and Cummings, 2007; Guimarães et al., 2008; Levy and Dubois, 2006; Starkstein and Leentjens, 2008; van Reekum et al., 2005). As a result, the reported associations between the lateral parietal cortex and apathy have been largely ignored and the cognitive basis of apathy symptoms due to impairments in this region have not been explained. To address this issue, we review evidence associating apathy with impairments in the lateral parietal cortex, and evaluate the cognitive and neural mechanisms that contribute towards reduced behavior. Our review suggests that changes in the lateral parietal cortex affects internal generation of motor intent, which underlies this subtype of apathy. This region maintains a body schema that is maintained through sensorimotor transformations, which facilitates the intentional selection of effectors (parts of the body) for action initiation as well as attributing actions to oneself (sense of agency). The occurrence of these functions of higher order motor cognition in this region provides compelling arguments for its role in apathy. We consequently propose that deficits in volitional processes be included in cognitive models of apathy and that angular and supramarginal gyri dysfunction be included in neural models of apathy.

In the following sections, we review the state-of-the-art of apathy and its assessment, focus on evidence supporting the involvement of the lateral parietal cortex in apathy, evaluate the cognitive processes involved, and present a new model for apathy emphasizing the role of the angular and supramarginal gyri in the internal initiation of action.

2. Current understanding and assessment of apathy

Symptoms of apathy are common in several brain disorders such as in neurodegenerative conditions like Alzheimer’s disease (AD), Parkinson’s disease (PD), and fronto-temporal dementia (FTD), in stroke (or cerebrovascular accident), and in schizophrenia. In each of these disorders, apathy becomes increasingly prevalent and severe with disease progression (with the exception of stroke where symptoms may improve with functional recovery) (Dujardin et al., 2007; Geda et al., 2014; Landes et al., 2005; Starkstein et al., 2006). It is also important to note that apathy in neurodegenerative diseases is often comorbid with other neuropsychiatric syndromes, resulting in a complex clinical picture. In particular, apathy and depression can appear to be clinically similar, though their neural basis has been shown to be distinct.

Despite the clinical significance of apathy, its definition is not clearly established. Proposed definitions include a lack of motivation (Marin, 1996; Robert et al., 2002; Starkstein and Leentjens, 2008), reduced initiative (Sockel et al., 2006), and persistent lack of interest, emotion, and/or concern (Cummings et al., 1994). While these definitions aim to capture the basis of apathy, the overt signs of apathy converge upon a paucity of self-generated or environment-induced goal-directed behaviors. Recently, consensus criteria were proposed wherein apathy is diagnosed by the loss of motivation and requires impairment in two of the three dimensions of behavior, cognition, and emotion (Robert et al., 2009). These symptoms must impair day-to-day functioning, and occur in the absence of other explanatory conditions such as physical or motor disabilities and loss of consciousness. The three clinical domains include the following: 1) reduced environment-stimulated actions; 2) reduced goal-directed cognition due to loss of ideas and curiosity in routine or new events, which includes spontaneous ideas, in the environment out of one’s interest, or social and
personal interests; and 3) reduced emotions, either spontaneous or evoked by external events. Any of these changes must not be due to other obvious causes such as motor disabilities, impaired consciousness or substance-induced states.

The three-domain diagnostic criteria are consistent with neural models of apathy that favor a three-factor differentiation of neural circuits (Brown and Pluck, 2000; Levy and Dubois, 2006). However, it must be noted that the three clinical domains and three neural circuits are not directly linked. Brown and Pluck (2000) described three cortico-subcortical loops that were proposed to underlie motivational deficits. These include a ‘motor’ circuit linking the primary and secondary motor cortex with the ventro-anterior thalamus and putamen, a ‘cognitive’ circuit linking the dorsolateral prefrontal cortex with the ventro-lateral/mediodorsal thalamus and caudate nucleus, and an ‘affective’ circuit linking the anterior cingulate cortex and orbitofrontal cortex to the mediodorsal thalamus, ventral pallidum, and ventral striatum. Levy and Dubois (2006) put forward a similar classification comprising of – an ‘emotional-affective’ subtype due to deficits in the orbital and medial prefrontal cortex, ventral striatum, and ventral pallidum; a ‘cognitive’ subtype due to deficits in the dorsolateral prefrontal cortex, caudate nucleus, substantia nigra, and thalamic nuclei; and an ‘auto-activation’ subtype with deficits in the medial prefrontal cortex and striato-thalamic regions. As stated above, neither model accounts for the empirical correlations with the lateral parietal cortex.

Similar to the definition of apathy, its assessment has also undergone refinement over time. Several instruments have been put forth to measure apathy in clinical settings. The most commonly used instruments include the apathy evaluation scale (AES) (Clarke et al., 2007), Lille apathy rating scale (LARS) (Sockeel et al., 2006), apathy scale (AS) (Starkestein et al., 1992), and apathy inventory (AI) (Robert et al., 2002). Other commonly used instruments that assess multiple behavioral symptoms include the neuropsychiatric inventory (NPI) (Cummings et al., 1994), frontal systems behavioral scale (FrSBe) (Grace et al., 1999), unified Parkinson’s disease rating scale (UPDRS) (Goetz et al., 2008) and positive and negative syndrome scale (PANSS) (Kay et al., 1987). Some of these instruments like the NPI, which is used most widely, simply indicate the presence or absence of apathy (and severity if present), others such as the AS, AI, and AES quantify the severity, and some like the LARS interrogate several domains of behavioral change.

The presence of sub-types in apathy has been repeatedly suggested (Brown and Pluck, 2000; Levy and Dubois, 2006; Marin, 1990; Starkestein and Leentjens, 2008; Stuss et al., 2000; van Reekum et al., 2005). However, questionnaires used to assess apathy do not typically identify these sub-types, or only attempt to do so in a limited way. The AES and the NPI are most commonly used but do not categorize symptoms into sub-types of apathy. The AI aims to identify the three standard sub-types but the symptoms for this classification are assessed with a limited number (2–3) of questions (Robert et al., 2002). The LARS uses a more extensive questionnaire compared to the AES and AI, consisting of 33 items in 9 domains and yields scores for four categories – intellectual curiosity, emotion, action initiation, and self-awareness (Sockeel et al., 2006). It has been mainly used to characterize apathy in patients with Parkinson’s disease. To our knowledge, the neural correlates of each category have not been reported.

3. Association between the lateral parietal cortex and apathy across disorders

In imaging studies across disorders, apathy is associated with deficits in multiple brain regions (Kos et al., 2016), with the most common region being the dorsal anterior cingulate cortex (dACC) (McIntosh et al., 2015; Pagonabarraga et al., 2015; Theleritis et al., 2014). However, as noted by Stella et al. (2014), apathy is also associated with other brain regions. Besides the dACC, apathy has been associated with deficits in sub-cortical regions, orbito-frontal cortex, and dorsolateral prefrontal cortex [See (Tekin and Cummings, 2002) for a discussion on the accompanying cognitive deficits]. Briefly, symptoms of apathy in these conditions can be divided into subtypes such as emotional (or affective), cognitive, and auto-activation deficit, depending on the affected circuits. Furthermore, the parent disorder may also indicate the likely mechanism such as in PD where loss of initiative is linked to dysfunction in the basal ganglia – prefrontal cortex circuits.

In addition to fronto-subcortical circuits, apathy has been linked to the lateral parietal cortex in a third of the studies on neurodegenerative disorders and in about 14% of studies on psychiatric disorders (Kos et al., 2016). This association is present across imaging modalities including structural, metabolic, and functional imaging and is discussed below for the different clinical conditions. Fig. 2 shows the location of regions (in the Montreal Neurological Institute atlas space) from studies associating apathy with the lateral parietal cortex. As recent reviews have covered neuroimaging findings related to apathy (Kos et al., 2016; Raimo et al., 2018; Starkstein and Brockman, 2018; Stella et al., 2014; Theleritis et al., 2014), we selectively review studies that concern apathy-associated changes in the lateral parietal lobe. We included such studies found with a systematic search by Kos et al. (2016) and further extended the search from April 2015 until October 2018 limited to the parietal cortex. The search terms ‘apathy OR avolition OR abulia’ or amotivation AND magnetic resonance imaging (MRI), positron emission tomography (PET) (and other imaging methods) AND Parietal’ were used in the PubMed database. Our extended search found 19 studies, of which six were original research studies in humans with sample size of 12 or more, with a clear description of inclusion criteria for apathy, and apathy was associated with the lateral parietal cortex. In total, 22 studies were found and are described below.

3.1. In Alzheimer’s disease

In AD, a progressive decline in cognitive functions is accompanied or in some cases, preceded by behavioral changes (Geda et al., 2008; Pietrzak et al., 2012). Apathy is the most common behavioral change in AD and when present in the prodromal stage, it increases the risk of disease progression (Peters et al., 2013; Rosenberg et al., 2013). Investigating the neural correlates of apathy, Ott et al., (1996) reported reduced cerebral perfusion in the right posterior temporal and parietal cortex in association with apathy in AD patients. Moreover, global...
cognition (measured using Mini-Mental State Examination) was not associated with perfusion in these regions or with apathy, suggesting that symptoms of apathy are not captured by cognitive measures and also the associated brain regions may not necessarily overlap. In another study of neuropsychiatric symptoms in seventy AD patients treated with donepezil (a cholinesterase inhibitor), similar findings were reported (Tanaka et al., 2004). In patients who had worse NPI scores especially due to increased severity of apathy after 12 weeks of treatment, blood flow was reduced in the left inferior parietal lobule (Brodmann Area (BA) 39) when compared to a group who did not show any change in NPI scores. The surrounding regions – left and right middle temporal gyrus (also BA 39), left superior temporal gyrus (BA 22), and left superior parietal lobule (BA 7) also showed reduced perfusion albeit to a lesser extent.

In addition to reduced blood flow, the AES score was found to be associated with reduced cortical thickness of the inferior temporal cortex in patients with mild cognitive impairment (MCI) (Guercio et al., 2015). In other tested regions, a weak inverse relation was found with the thickness of the ACC whereas no association was found with the supramarginal gyrus and medial orbitofrontal cortex. The inferior temporal cortex was also predictive of increased severity of apathy symptoms on the NPI in MCI and AD patients in a study which investigated the same regions (Donovan et al., 2014). In 402 subjects (cognitively normal, MCI, and AD) drawn from the same cohort, hypometabolism in the supramarginal gyrus (BA 40) was associated with higher apathy scores on the NPI over time (Gatchel et al., 2017). Regions included in this analysis were orbitofrontal cortex, anterior cingulate cortex, inferior temporal cortex, and the posterior cingulate cortex, where hypometabolism at baseline was associated with apathy severity at baseline.

Furthermore, changes in white matter in the lateral parietal cortex have also been associated with apathy in AD. Apathy was diagnosed with similar criteria as those described above and quantified with the AS (apathy scale) whereas depression scores were obtained with the Hamilton Depression Rating scale. Damage in the white matter of the right parietal lobe in the form of hyperintense lesions, indicative of vascular pathology, was found to be increased in probable AD patients with apathy and comorbid depression (Starkstein et al., 2009). In these patients, apathy without depression was also related to higher white matter changes in the frontal lobe. Using diffusion imaging to characterize nerve tracts in twenty one AD patients who were administered the AS, Ota et al. (2012) found that apathy severity was associated with reduced fractional anisotropy, indicative of damage to nerve fibers, in the bilateral parietal cortices, besides the right ACC and right thalamus. Measures of diffusion such as fractional anisotropy can be used to delineate major white matter tracts. In one such analysis, the right superior longitudinal fasciculus, which carries nerve fibers between the frontal and parietal cortex, was shown to have reduced integrity in association with apathy severity in AD patients (Hahn et al., 2013). In this study, apathy was diagnosed according consensus criteria described above and quantified using the AI (apathy inventory). All scores were also inversely correlated with cingulum bundle and uncinate fasciculus.

The findings of impaired structural connectivity are supported by a recent study where affective symptoms, particularly apathy (measured with the NPI), were associated with reduced functional connectivity in the fronto-parietal network (correlation between time-courses of activity in brain regions) in patients with MCI (Munro et al., 2015). No association was found with the DMN, and dorsal and ventral attention networks. Finally, in amnestic MCI patients, our group found that metabolite levels on magnetic resonance spectroscopy were altered in association with AES (apathy evaluation scale) scores only in the right temporo-parietal cortex and not in the dorsal ACC, right dorsolateral prefrontal cortex, or the posterior cingulate cortex (Tumati et al., 2018). Subjects were diagnosed with apathy according to the consensus criteria. Thus, a number of studies in AD patients have reported apathy to be associated with deficits in the lateral parietal and temporal regions, particularly in the right hemisphere.

3.2. In Parkinson’s disease

In PD, atrophy of dopaminergic neurons in the brainstem is accompanied by characteristic motor symptoms of tremors and rigidity. In addition to motor symptoms, neuropsychiatric features are also common in PD (Chaudhuri et al., 2006). Symptoms of apathy are diagnosed in a quarter to one-third of patients in the early stages of the disease, and with progressive worsening, this proportion increases (Pagonabarraga et al., 2015). Like in AD, apathy in PD is also associated with changes in multiple brain regions with prefrontal-subcortical circuits being affected most often (Pagonabarraga et al., 2015). However, apathy has also been associated with changes in the lateral parietal cortex. In early PD patients, Reijnders et al. (2010) found reduced grey matter density in a number of regions including the bilateral inferior parietal lobes to be associated with apathy. In this study, apathy was characterized with multiple assessment tools (AES, LARS, and NPI), and the apathy score derived with each tool was found to be associated with nearly identical brain regions (Reijnders et al., 2010). The strongest association in this study was found in the precentral gyrus (BA 6), followed by the inferior parietal cortex (BA 40). Other regions associated with apathy scores from all three scales were the inferior frontal gyrus (BA 13, 44 & 47), insula (BA 13), and posterior cingulate cortex (BA 31, 30).

Consistent with the above study, atrophy in the inferior parietal cortex (BA 40) was also present in a non-depressed PD cohort with apathy (diagnosed by consensus criteria) (Martínez-Horta et al., 2017). Other regions with lesser atrophy included the post-central gyrus, pars opercularis, nucleus accumbens, supplementary motor area, inferior orbitofrontal cortex, and superior parietal lobule. Further supporting this relation, atrophy in the inferior parietal lobule (BA 40) along with the precuneus (BA 7) was higher in the apathy group, who were diagnosed with a AS score more than 14 and without depression in PD (Shin et al., 2017). In another study investigating metabolic changes in early stages of PD, apathy was found to be associated with reduced glucose metabolism in the right inferior parietal lobule (BA 40) and left superior temporal gyrus (BA 39) (Huang et al., 2013). In this study, the AES score strongly correlated with higher metabolism in the bilateral anterior cingulate cortex (BA 32) and bilateral orbitofrontal lobe (BA 10), and lower metabolism in tempo-parietal regions. Notably, reduced motor functions (measured with UPDRS part III) were also associated with reduced metabolism in the bilateral inferior parietal lobule (BA 39).

Results from a study using functional magnetic resonance imaging acquired under resting conditions also showed an association between the LARS score and the amplitude of the fMRI signal in the left inferior parietal lobule (BA 40) in PD patients. In this study as well, the motor score (UPDRS part III) was associated with same fMRI measure in the angular gyrus (BA 39) (Skidmore et al., 2013). These regions were among a number of other regions associated with the LARS (middle occipital gyrus (BA 10), supplementary motor area (BA 6), middle frontal gyrus (BA 6), cerebellum, fusiform gyrus (BA 37), and subgenual cingulate (BA 25)) and UPDRS part III (putamen, cerebellum, and others). Together, these findings suggest that dysfunction in the inferior parietal lobule (BA 39/40) plays a role in apathy in PD and that reduced motor function may mediate this association.

3.3. In fronto-temporal dementia

Apathy is also a common symptom of FTD, which is characterized by atrophic changes in the frontal and temporal lobes of the brain. Symptomatically, behavioral disturbances are prominent in FTD, which occur either in the form of increased behavioral activity such as loss of inhibition, inappropriate behavior, and repetitive actions, or manifest as reduced self-initiated behavior (i.e., apathy) (Méndez et al., 2008).
Both clinical presentations of FTD are correlated with atrophic changes in the frontal lobes. However, similar to AD and PD, apathy in FTD has also been associated with the lateral parietal cortex. In sixty-two FTD patients, the severity of apathy, as measured by the apathy sub-scale of the FrSBe, was associated with reduced gray matter density in the lateral frontal cortex (BA 45, where the strongest association was found, BA 8, 9, 10, 11, 32, 45, 46, 47) as well as the right inferior parietal lobule (BA 40) (Zamboni et al., 2008).

Similar results were also found in a smaller sample of patients with the behavioral variant of FTD where the AES score was based on caregivers’ report and was associated with reduced gray matter density in the right temporoparietal junction (BA 39, 40) besides the caudate, right temporal gyri (BA 21/37), and left frontal operculum/insula (BA 44, 45) (Eslinger et al., 2012). In a retrospective study of twenty-five late-onset FTD patients, patients with apathy (n = 13, classified according to a clinical evaluation) showed hypometabolism in the bilateral inferior parietal lobule (BA 40) and the lateral frontal cortex (BA 44, 47, 10), and atrophy in the left inferior parietal lobule (BA 40) and frontal regions (BA 9, 10, 44) compared to healthy control subjects (Morbelli et al., 2016). In both modalities, the maximum difference in the inferior parietal lobule was as large as the frontal regions compared to control subjects.

3.4. In stroke, Huntington’s disease and schizophrenia

The lateral parietal cortex is also associated with apathy in post-stroke syndromes. In a three-year follow-up of a single subject who developed apathy following a stroke, functional connectivity of the inferior parietal lobule along with that of the ACC was found to be altered (Siegel et al., 2014). The typical positively correlated activity between the inferior parietal lobule and medial frontal brain regions was reversed and a normal positive correlation with other brain areas was reduced. In this single case study, apathy was associated with changes in multiple cortical and subcortical areas. That apathy is associated with multiple regions of the brain including the lateral parietal cortex is also borne out by a study in a large sample of stroke patients (Yang et al., 2015). The AES score was negatively correlated with structural connectivity (measured by diffusion imaging) in 24 regions across the brain, among which the strongest negative correlation was found with the right supramarginal gyrus and precentral gyrus. In a study of patients with mild Huntington’s disease, hypometabolism in the superior parietal cortex and atrophy in the temporal gyrus (among a number of cortical and subcortical regions) were associated with the severity of apathy, measured with the Problem Behaviors Assessment interview (Martinez-Horta et al., 2018). In schizophrenia patients, using task-based functional imaging Liemburg et al. (2015) found that brain activation was reduced in the inferior parietal lobule while performing the Tower of London task in association with greater apathy as measured with a proxy score derived from the PANSS. Other regions including the right middle temporal gyrus, precuneus, paracentral lobule, and thalamus were also associated with apathy and other task conditions.

3.5. Summary of findings and their relation to neural models of apathy

In the above-mentioned studies, symptoms of apathy in brain disorders with varying etiologies were associated with altered structure, function and metabolic activity in the lateral parietal cortex. Within the lateral parietal cortex, the inferior parietal lobule was most often associated with apathy. The peak regions in the IPL that were associated with apathy in some studies could be further assigned to cytoarchitecturally-delineated sub-regions (Caspers et al., 2008) such as Area PF (Zamboni et al., 2008), Pfr (Reijnders et al., 2010), PFcm (Eslinger et al., 2012; Martinez-Horta et al., 2017), PGa (Tanaka et al., 2004), PGp (Huang et al., 2013), and PFM (Huang et al., 2013). In addition, Area hLP1 (Morbelli et al., 2016; Shin et al., 2017), hLP2 (Morbelli et al., 2016), and hLP3 (Liemburg et al., 2015) along the surrounding intraparietal sulcus were also associated with apathy.

Despite the association of apathy with the lateral parietal cortex in a number of studies including differences in the measurement of apathy, these findings were not extensively discussed or considered to be of significance. A likely reason for this may be that in a majority of these studies, apathy was associated with multiple brain regions including the dorsal ACC, medial prefrontal cortex or basal ganglia. The consistent association of apathy with these regions lends support to neurocognitive models where deficits in the prefrontal cortex – basal ganglia circuits are proposed to be the neural basis of apathy (Brown and Pluck, 2000; Guimarães et al., 2008; Levy and Dubois, 2006; van Reekum et al., 2005). These models also describe the cognitive mechanisms supporting goal-directed behavior where apathy may result either due to an inability to evaluate the reward potential of an action (behavioral apathy, consistent with deficits in the medial prefrontal cortex), or deficits in executive functions (cognitive apathy, consistent with deficits in the lateral prefrontal cortex) or deficits in spontaneous activity (auto-activation deficit, consistent with deficits in the basal ganglia) (Brown and Pluck, 2000; Levy and Dubois, 2006).

In the next section, we highlight the role of regions within the inferior parietal cortex in voluntary actions, then focus on the processes of higher-order motor control in the broader lateral parietal cortex, and finally show how these processes are invoked in goal-directed actions. The role of these processes and their interrelationship in voluntary action is derived from relevant literature from cognitive neuroscience as well as lesion studies. Based on the findings, we describe how deficits in volitional behavior lead to apathy.

4. The role of the lateral parietal cortex in generating intentional behavior

The lateral parietal cortex is linked to diverse cognitive processes such as attention, working memory, spatial cognition, and social cognition (Cabeza et al., 2012; Humphreys and Lambon Ralph, 2015). However, its plausible role in generating motor intent (Desmurget et al., 2009) may be particularly relevant to the development of apathy.

Goal-directed behavior implicitly involves the intentional initiation and regulation of actions. However, neural models of goal-directed behavior seldom take into account the ability to initiate actions, perhaps because this ability is rarely affected. In its intact functional state, initiating actions may be seen as an automatic process that requires little cognitive effort, and hence, may not be particularly relevant in understanding the neural mechanisms that support the complex process of setting goals, planning appropriate paths to the goal, and monitoring the process. However, apathy may be one such condition where the inability to intentionally initiate behavior is thought to underlie its symptoms. Levy and Dubois (2006) proposed to define apathy as ‘the quantitative reduction in self-generated voluntary and purposeful behavior’. The association of the lateral parietal cortex with apathy and as well as with volition provides a basis for examining the mechanism of apathy in such cases.

In the following two paragraphs, we elaborate on the role of the inferior parietal lobule in generating motor intention, its involvement in sense of agency, and the integration of these functions with higher-order motor control. Along this line, we review the literature to show that generating intentional action is not an isolated function supported by this region but naturally emerges from the maintenance of a body schema in the broader lateral parietal cortex which facilitates higher-order motor control processes. This function of facilitating intentional motor control is elucidated with the help of functional impairments resulting from lesions in this region.

4.1. Intention and sense of agency as volitional processes

Volition encompasses temporally distinct concepts of an intention to
act, selection of an appropriate action, and attributing the outcome to the self-initiated action. Intentional actions, as opposed to simple or complex habitual movements, are particularly relevant for goal-directed behavior. In apathy, assessing whether patients lack initiative in performing activities directly relates to the concept of volition. Studies over two decades have extensively investigated the neural basis of volition (see Haggard, 2018 for a detailed discussion) and evidence converges on the inferior parietal lobule as the key region for volition-linked processes in the brain (Desmurget and Sirigu, 2012).

The intention to act can be detected prior to motor movements being initiated. First reported as fluctuations in brain activity on electroencephalographic recordings, the ‘bereitschaftspotential’ or readiness potential has been interpreted as neural activity that reflects motor preparation preceding movement or planning of an action (Kornhuber and Deecke, 1965). Such activity preceding an action can be recorded from multiple brain regions including the basal ganglia, pre-supplementary motor area, and the inferior parietal lobule (Colebatch, 2007; Kukleta et al., 2012). The basis for neural activity in the basal ganglia and pre-supplementary motor cortex in preparing for move can be explained by their direct role in the control of movement. The basal ganglia maintain tonic inhibition over the primary motor cortex, which is released from this inhibitory control by inputs from the pre-supplementary motor area. However, the detection of the readiness potential in the inferior parietal lobule before the onset of movements in less clear. Studies suggest that the inferior parietal lobule plays a role in the generation of intention to move (Sirigu et al., 2004). Patients with lesions in this region were found to be aware of the performed movement but were unable to recall if they were aware of the intention to move (Sirigu et al., 2004). The inability to experience intentions can lead to misattribution of the agent of the action. That is, the performed action is not experienced as self-initiated. Apraxic patients with parietal lobe damage show reduced ability to distinguish movements initiated by themselves from those of others (Sirigu et al., 1999). Moreover, even discriminating non-motor functions as being generated by oneself or by others may be affected due to deficits in this region. Plaze et al. (2015) found that schizophrenia patients with auditory-verbal hallucinations (misattributing the agent of thoughts) show altered morphology of the inferior parietal lobule. These findings suggest that the intention to act is experienced consciously as being self-initiated by neural processes in the inferior parietal lobule. The findings also suggest that intention-to-act and sense of agency are coupled and integrated during voluntary action.

A refined distinction between generating movements and their subjective experience in brain regions has been made by studies using brain stimulation (Desmurget et al., 2009; Douglas et al., 2015; Fried et al., 1991). These studies provide evidence for distinguishing the contribution of different regions to motor movements and volition. Using direct electrical stimulation of the cortical surface, Desmurget et al. (2009) found that stimulating the pre-supplementary motor area produced an inclination or urge to move a body part, such as the hand or lips, depending on the location of stimulation. As the strength of the stimulation was increased, actual movement of the corresponding body part occurred. A similar ‘urge to act’ was also produced on stimulating the inferior parietal lobule. A crucial difference between the two stimulation sites was that on supra-threshold stimulation of the inferior parietal lobule, subjects sensed movements in the corresponding body part despite the absence of any such movement.

Anatomically, the stimulation sites in the inferior parietal lobule that showed both conscious intention as well as the illusion of movement were found to lie along the border between the angular gyrus and the supramarginal gyrus. In contrast, stimulation of the mesial precentral area, a region close to motor areas, elicited compulsive feelings to perform an action. Importantly, the sensation of impending movement was not perceived as self-intentioned but as occurring without the subject’s control (Desmurget et al., 2009). Contrasting these outcomes, the inferior parietal lobule appears to be crucial to experiencing intention and perceiving a movement as self-initiated (even when a movement has not occurred), while the pre-supplementary motor area activates movement but does not contribute to their perception of it being self-initiated (sense of agency).

The association between intentional movement and the inferior parietal lobule is further supported in a recent study where transcranial magnetic stimulation over the angular gyrus was found to alter how early the intention of performing a movement was consciously experienced (Douglas et al., 2015). This study is in line with previous evidence showing that patients with damage to the angular gyrus in the inferior parietal lobule report a delay in experiencing motor movements until just before (~50 ms) an action is performed, as compared to healthy subjects (~250 ms) (Sirigu et al., 2004). It may be concluded that the strength of activity in the angular gyrus of the inferior parietal lobule affects the conscious perception of the intention to move, which may be necessary to link actions and outcomes to internally generated intentions.

Further evidence linking the inferior parietal lobule to sense of agency can be found in the results from Haggard and Cole (2007) who showed that this region is highly active when subjects recognize that observed outcomes were due to their own actions. Conversely, lower activity was found in this region when subjects perceived a dissonance between their actions and outcomes. Sense of agency may also be prospective, i.e., whether an action is attributed to oneself may be experienced before performing the action (Chambon et al., 2015). To test this hypothesis, neural activity in the inferior parietal lobule was disrupted using transcranial magnetic stimulation, which resulted in reduced perception of self-control on subsequent actions. This finding suggests that not only does activity in the inferior parietal lobule contribute to perceiving the intention to move but also in perceiving the degree of control over actions.

Strong evidence for the role of the inferior parietal lobule in volition is provided by rare circumscribed lesions that show symptoms that dissociate the usually tight link between the sense of intentionally producing actions and the actions themselves. The parietal variant of the alien hand syndrome typically results from a stroke in the angular gyrus. Patients with this syndrome present with complex goal-directed movements observed are less complex but produce a stronger sense of loss of ownership. In such cases, other accompanying symptoms such as hemispatial neglect and disordered body schema may occur (Hassan and Josephs, 2016). Thus, the alien hand syndrome shows that the angular gyrus may process intentional processing and receives feedback that may enable it to monitor the movement.

In the context of self-generated behavior, the alien hand syndrome suggests that the inferior parietal lobule contributes to the perception of motor movements as being intentional by integrating neural signals of motor preparation, initiation or execution with proprioceptive feedback of movement. Deficient integration of these processes may contribute to the loss of agency, particularly when such deficiency includes impaired matching of predicted sensory consequences of movement and the actual sensory feedback (de Jong, 2011). Indeed, neuronal mechanisms underlying intentional movement and sense of agency appear to be embedded in similar regions. Moreover, goal-directed behavior requires intentional direction of movements as well as recognizing the link between intention and action. Based on these studies, a model was proposed where the inferior parietal lobule sends sustained excitatory inputs to the supplementary and premotor areas in order to generate voluntary actions. Moreover, in this model the angular gyrus receives inhibitory feedback from the primary motor cortex after an action is executed (Fried et al., 2017).

S. Tumati et al. Progress in Neurobiology 175 (2019) 20–34
4.2. Higher-order motor control in the lateral parietal cortex

The volitional function attributed to the angular and supramarginal gyri are not isolated motor functions occurring in this region. As suggested by symptoms of disorders that affect the lateral parietal cortex, it is embedded within a wider framework of higher-order motor cognition. For example, apraxia is classically associated with this region and shows symptoms of inability to perform skilled movements. In Gerstmann’s syndrome, agraphia may occur simultaneously with left-right confusion. Thus, complex presentations that include disorientation of body schema, the sense of loss of body ownership, poor higher motor abilities, and other cognitive symptoms become manifest due to dysfunction in this region. Apraxia and hemi-spatial neglect are typically associated with the lateral parietal cortex, and their symptoms can help understand the mechanisms of motor control that are processed in this region.

Patients with apraxia are unable to perform skilled motor movements, in the absence of sensory, motor, or muscular disorders (Geschwind and Damasio, 1985). The ideational and iedo-motor forms of apraxia are particularly relevant to goal-directed behavior. Both subtypes involve transforming abstract concepts of an action to an precise execution of complex motor movements. While the definition and neural substrates of each subtype are debated (Buxbaum et al., 2014), ideational apraxia refers to the difficulty in generating complex movements when using an object, (De Renzi and Lucchelli, 1988) whereas iedo-motor apraxia refers to the difficulty in performing an imagined movement on command, i.e., pantomiming (De Renzi et al., 1980). Various models have been proposed to explain the observed deficits in ideational apraxia including loss of knowledge of object usage (De Renzi and Lucchelli, 1988), disordering of action sequence (Poeck and Lehmkuhl, 1980), and incorrect activation of relevant schemas and suppression of irrelevant schemas at appropriate times (Norman and Shallice, 1986). These models point towards deficits in specific stored action plans. Ideomotor apraxia, on the other hand, is considered more sensitive to motor control since the absence of a tool or object deprives sensory input, which likely supports the execution of actions (Goldenberg et al., 2004). This sensitivity has a direct bearing on goal-directed behavior since it implies that pantomiming requires intentionally activating a specific action sequence towards an imagined goal while constraining other stored schemas resulting in accurate and meaningful motor movements.

Models of ideomotor apraxia (Buxbaum et al., 2000; Cubelli et al., 2000; Gonzalez Rothi et al., 1991) broadly involve conversion of action semantics and gesture patterns to motor output. Buxbaum et al. (2000) emphasized the dynamic regulation of intrinsic body schema in the production of gestures. The production of an intentioned action fails due to an inability to provide a continually updated body schema. In case of actual tool use, deficient interaction between the action schema and body schema is compensated by sensory and visual feedback. Another view suggests that deficits arise due to difficulties in selecting the appropriate action schema, rather than deficits in or between action and body schemas (Bekkering et al., 2005). This view regards imitation as a goal to be achieved by selecting the appropriate action schema. A large voxel-based lesion-symptom mapping study found that pantomiming was more strongly associated with lesions in the posterior temporal lobe, while imitation of meaningless gestures was more strongly associated with lesions in the parietal lobe (Buxbaum et al., 2014).

Thus, findings from studies on apraxia suggest that the lateral parietal cortex and surrounding regions support motor planning and execution by processing motor and body schemas of intentional actions. Similar to apraxia, neglect is also classically associated with damage to the parietal lobe (Azouvi et al., 2002; Hillis et al., 2005; Mort et al., 2003; Vallar and Perani, 1986) and the superior temporal lobule (Karnath et al., 2004; Ringman et al., 2004). Patients fail to attend to stimuli present on the contralesional side, in the absence of sensory and motor deficits (Mesulam, 1999; Vallar, 1998). This complex condition indicates that for motor cognition, the dysfunction of motor and body schemas, which are seemingly affected in apraxia, maybe further linked to the neural representation of space. Studies show that an egocentric (spatial organization of objects with respect to the body) and an allocentric (spatial organization of objects with respect to one another) map are encoded by the lateral parietal cortex and the temporal lobe, respectively (Hillis et al., 2005; Ota et al., 2001; Verdon et al., 2010). Several theories have been put forth for this purpose including selecting the objects to be perceived (Bartolomeo and Chokron, 2002), the direction and maintenance of attention (Corbetta and Shulman, 2002), deficits in spatial working memory (Pisella and Mattingley, 2004; Vuilleumier et al., 2007), and deficits in motor control involved in initiation of arm (or eye) movement (Kubanek et al., 2015; Mattingley et al., 1998). Though the neural basis of neglect is not clear (McGlinchey-Berroth et al., 1996; Molenberghs and Sale, 2011; Rorden et al., 2012), the symptoms show that generating action requires normal encoding of spatial features in the postero-lateral regions of the cortex.

Damage to the lateral parietal cortex can also result in complex syndromes with varying symptoms, showing that this region is involved in diverse cognitive processes such as attention, working memory, spatial cognition, and social cognition (Cabeza et al., 2012; Humphreys and Lambon Ralph, 2015). For example, in Gerstmann’s syndrome, lesions in the inferior parietal lobule and particularly in the angular gyrus (Mayer et al., 1999; Morris et al., 1984; Roux et al., 2003) result in acalculia, finger agnosia, agraphia and left-right confusion, which may result from a disordered mental body schema (Gerstmann, 1930). While it is not likely that apathy associated with changes in the inferior parietal lobule is associated with diverse cognitive deficits or with any rare syndromes, the functional deficits in these disorders suggest that this region may integrate multiple processes of selecting effectors of action, a dynamic body schema, and action schemas necessary for generating and regulating goal-directed actions.

5. Integration of motor cognition with goal-directed behavior

In Section 1, we introduced goal-directed behavior as the key cognitive framework that is disrupted in apathy. In Section 4, we posited that deficits in volitional processes occurring in the inferior parietal lobule result in apathy, which we based on symptoms observed in apathy and the functions most likely to underlie these symptoms. We further described the deficits in motor control that result from deficits in the lateral parietal cortex and neighboring temporal regions, inferring that volition is embedded within a broader framework of intentional motor control. On the basis of these studies, we concluded that the maintenance of a body schema in this region or its continuous updating through somatosensory (proprioceptive) feedback are key processes that facilitate the generation and regulation of action. These processes allow control of intentional actions, which is essential to perform goal-directed behavior. To further describe the integration of higher-order action control with goal-directed behavior, we delve into the cognitive processes associated with this region in the healthy state. Models of goal-directed behavior provide a framework of cognitive elements that are needed for successfully reaching a predetermined end point (Brown and Pluck, 2000; Verschure et al., 2014). A key initial step in such a framework is the formation of an intent to act, driven by external or internal cues. A second component includes planning, which can be broken down into the representation of a goal, determining a sequence of actions aimed towards the goal, and selection and timing of actions during execution. The final component entails the initiation and execution of actions. In addition, a set of supervisory processes is essential for ensuring that actions are directed towards the goal, and if not, to incorporate necessary adaptations into the action sequence. Verschure et al., 2014 describe these processes in terms of ‘what’, ‘why’, ‘when’, ‘where’, and ‘how’. In other words, the ‘why’ component forms
the goal and the reason for its choice; the ‘what’ component represents the broad plan of action; the ‘when’ and ‘where’ components reflect the spatiotemporal aspects of the actions; the ‘how’ component describes the detailed motor sequences to be performed (Verschure et al., 2014). Notably, the authors distinguish between internal and external cues of goal-directed behavior, with the former relying on longer time-scales, driven by memory and internal states.

5.1. Regulation of intentional goal-directed actions: Attentional control, Action planning and Regulation of motor movements

Goal-directed actions require top-down attentional control, spatial representation, and execution of complex motor movements, functions which are ascribed to the superior parietal lobule and intraparietal sulcus (Andersen and Cui, 2009; Corbetta and Shulman, 2002; Gallivan et al., 2011). For performing a series of actions, these functions must be integrated (Humphreys and Lambon Ralph, 2015). Thus, a cross-modal functional integration may occur in the following form: mental simulations are performed of planned actions, an optimum action plan is selected and execution of the action sequence is initiated. The visual and somatosensory feedback from actions are evaluated and the motor plan is continuously updated to maintain a trajectory towards the goal (Battaglia-Mayer et al., 2014). The superior parietal lobule is activated during top-down tasks (Corbetta et al., 1995), which is paired to preformed responses such as when searching for specific visual cues presented among a set of distractors (Corbetta and Shulman, 2002). Top-down attention is also necessary for spatial working memory, which maintains a representation of salient cues for a short duration after the cue is changed or removed (Awh and Jonides, 2001). Activity in this region is also implicated in selecting motor actions, updating of the plan of action and in tracking outcomes of the action (Caminiti et al., 2010; Desmurget et al., 1999). This region is also active during sequential movements, whether self-performed, imagined/planned, or performed by others, which are achieved through sensorimotor integration (Cui, 2014).

Whereas the superior parietal lobule is more strongly linked to spatial orientation, planning, and maintenance of attention on a task, activity along the intraparietal sulcus is associated with effectors such as in the dynamic adjustment of eye and hand movements during a task (Gallivan et al., 2011; Glover, 2004; Tunik et al., 2005). The former is suggested to rely on multiple sensory and cognitive inputs while the latter guides actions towards the goal (Glover, 2004). Besides externally-directed planning, action performance also involves (internal) preparation of the body for executing the requisite motor plan. Pertaining to execution of actions, Beudel and de Jong (2009) contrasted two visuo-motor tasks and found that the superior parietal lobule was activated only when an instructed finger was to be guided to a fixed button as compared to when an instructed button was to be pressed with a fixed finger. After the initiation of planned actions, the intraparietal sulcus regulates spatial and temporal adjustments in movements to reach a target (Tunik et al., 2005). To support dynamic adjustments of movements, the intraparietal sulcus is suggested to store goals of an action, to which the executed action and its outcomes are compared, and in case of a mismatch, corrective movements are initiated (Tunik et al., 2007). This inferential view is supported by evidence that the intraparietal sulcus is active in the selection of a movement. When presented with alternative response choices, encoded in the lateral frontal brain regions, the intraparietal sulcus signaled the selection of the appropriate choice (Muhle-Karbe et al., 2014). When activity in this region was disrupted by transcranial magnetic stimulation in close temporal proximity to selection of the appropriate response, more errors occurred as compared to control subjects. Furthermore, this study aimed to distinguish the role of the inferior frontal gyrus in this process, and found it to be associated with updating of task goals, whereas the intraparietal sulcus was associated with responses to the task (Muhle-Karbe et al., 2014). Similarly, the initiation of adjustments to an action were disrupted by transcranial magnetic stimulation to the intraparietal sulcus but had no effect if stimulation was applied after adjustments were already initiated (Glover et al., 2005). An alternative view suggests that the superior parietal lobule and intraparietal sulcus both store representations of motor plans, but the latter is active earlier than the former (Verhagen et al., 2013). Taken together, these regions appear to contribute to motor cognition by dynamically regulating goal-directed action: movements are planned by selecting the effector (Beudel and de Jong, 2009), the appropriate action is chosen from multiple responses encoded in the lateral prefrontal cortex (Muhle-Karbe et al., 2014), and then spatial and temporal control over motor movements is maintained so that they remain oriented towards intended goals (Glover et al., 2005; Tunik et al., 2007; Verhagen et al., 2013). Thus, the superior parietal lobule and the intraparietal sulcus together translate abstract goals represented in the frontal lobes to specific motor plans and regulate their execution (Muhle-Karbe et al., 2014).

These results show how the lateral parietal cortex presumably regulates goal-directed actions. While these functions play an important role in controlling movements, their dysfunction results in symptoms of apraxia and neglect but not of those seen in apathy. A key feature of apathy is the difficulty experienced by patients in initiating behavior out of their own volition. Thus, the processes described above are essential for higher-order control of movement but are unlikely to be directly affected in apathy since the execution of actions is usually unaffected in these patients as seen from their ability to perform actions when asked to do so. Instead, it is more likely that in inferior parietal lobule-associated apathy, internal generation of cues for action are impaired or the initiation of action is affected. From the perspective of volitional control, the inferior parietal lobule may act as a gating mechanism that allows action to be initiated and monitors the resulting movement.

6. Self-generated behavior: actions in response to internal cues

Cognitive models of goal-directed behavior and cognitive control of action describe the necessary chain of processes but the neural mechanisms that facilitate the transformation of internal states to actions are less clear. Both types of models do not differentiate between processes that result from external or internal stimuli. That is, these models describe a common pathway of goal-directed behavior. This distinction is especially pertinent in case of volition and apathy where actions must be initiated in the absence of an external stimulus. The external environment in this case provides a framework of possible actions but does not determine the initiation of the action. The action must be determined by the internal state of the individual, which includes recruitment of one’s body schema to facilitate the appropriate selection of an effector system. The inferior parietal lobule may be functionally well-located for this role due to its participation in large-scale brain networks as described below.

Functional brain networks comprise of distant regions that show spontaneous and coordinated neural activity (Fox et al., 2005). This functional organization of the brain is based on a framework of structural connections and is present in states of rest as well as sleep (Greicius et al., 2009). The default mode network (DMN) comprises of midline structures in the anterior and posterior cortical regions, and the inferior parietal lobule of the lateral parietal cortex (Raichle et al., 2001). Also termed the task-negative network, the DMN is more active when individuals are not engaged in any task or are asked to not think of anything in particular. When performing cognitively demanding tasks that require problem solving and working memory, the DMN typically shows reduced activity while areas in the lateral frontal cortex and lateral parietal cortex are activated (Fox et al., 2005). The task-positive regions show anti-correlated activity with the DMN, and are segregated into the fronto-parietal control network (FPNC) consisting of regions in the rostrolateral prefrontal cortex and the inferior parietal
lobule and active when performing executive functions (Vincent et al., 2008), and the dorsal attention network comprising of the superior precentral gyrus and the superior parietal lobule. Both networks are active during tasks requiring sustained attention (Fox et al., 2006). The specialized cognitive processing of internally- and externally-oriented processes in individual networks provides a basis for a neurocognitive framework for goal-directed behavior.

When performing cognitive tasks, brain networks function as segregated but not isolated systems and cognitive performance is supported by network connectivity (Cole et al., 2014; Krienen et al., 2014). Such interactive functional networks may be especially crucial for goal-directed cognitive activity. Spreng et al. (2010) investigated the activity of the DMN and the FPCN under two conditions requiring autobiographical planning based on personal goals related to debt and employment, and an externally-directed visuo-spatial planning task (the tower of London test). The FPCN was found to interact with the DMN and dorsal attention networks in the self-related and externally-directed conditions, respectively. The authors concluded that the FPCN ‘may flexibly couple with the default and dorsal attentional networks’ and act as ‘a cortical mediator linking the networks in support of goal-directed cognitive processes’. Thus, these results support the view that internally- and externally-directed cognition relies on interactions between the FPCN and DMN, as well as FPCN and dorsal attention network, respectively.

Among the regions forming these large scale networks, the inferior parietal lobule is uniquely located to participate in the internally-oriented DMN and the externally oriented FPCN. Its further functional subdivision into regions that uniquely participate in the either the DMN or the FPCN is not clearly demarcated (Humphreys and Lambon Ralph, 2015). It also interacts with the superior parietal lobule and intraparietal sulcus of the dorsal attention network (Vincent et al., 2008; Spreng et al., 2010). The supramarginal gyrus of the inferior parietal lobule has been shown to have overlapping activity with the DMN, dorsal attention network and salience network (comprising of the dorsal ACC and insula) (Braga et al., 2013). The close functional relationship of the inferior parietal lobule with multiple networks with distinct functions may be linked to its putative role in initiating goal-directed actions as distinct cognitive processes must ultimately regulate behavior. The functional connectivity of the inferior parietal lobule with the salience network, FPCN, and dorsal attention network may allow it to participate in externally-oriented processing, and at the same time, as part of the DMN, it may participate in internally-oriented processing. This bridging function of the inferior parietal lobule may facilitate the guiding of externally-oriented goal driven actions by the internal state. Based on this inference, a neural framework for cognitive models of goal-directed behavior can be delineated.

Midline structures in the cortex are associated with self-relevant processes (Northoff et al., 2006). Their integrated function as part of the DMN may determine the internal state with the subgenual ACC and medial prefrontal cortex evaluating reward potential of stimuli, and the posterior cingulate cortex and precuneus processing autobiographical information. The precuneus has been directly linked to action performance. Brain activation in the precuneus predicted the action to be performed, and occurred considerably before subjects reported awareness of their intention to perform a specific action. Increased activity in this region occurred several seconds prior to the motor response (Soon et al., 2008), and prior to subjects reported becoming aware of the choice (Soon et al., 2013). Moreover, the report of awareness of movement intention paralleled increased activity in the angular gyrus. This finding supports a possible role for the posterior cingulate cortex/precuneus in evaluating the self-relevance of an action and the inferior parietal lobule in triggering planning and performance of actions after a future desired state (goal) has been affirmed. In a broader context, connectivity between these regions enables integration of self-related processes with performed, imagined, and observed actions (Buckner and Carroll, 2007; Farrer et al., 2008; Lou et al., 2004).

Functional connectivity between the supramarginal gyrus and the salience network is of particular interest for goal-directed behavior. Beудel and de Jong (2009) asked participants to select one of four buttons representing a free external choice, and found the dorsal ACC and the inferior parietal lobule were both activated, whereas when subjects were asked to choose a finger to press a specific button, representing a free internal choice, only the inferior parietal lobule was activated. A similar study used a finger-tapping task where subjects had to either tap a specific spot or choose to tap one of the three spots (Zhang et al., 2012). Contrast the choice condition with the specified condition showed increased activation in the lateral parietal cortex supporting this region’s role in intentional actions. In this study also, the dorsal ACC (and supplementary motor cortex) was found to be associated with action selection under both conditions. Similarly, another study also found that internally-driven movements were associated with the supramarginal gyrus (among other regions) (Ariani et al., 2015). Moreover, the broader temporo-parietal cortex was found to be associated with abstract planning of movements in externally- and internally-directed tasks. These results suggest that the dorsal ACC and inferior parietal lobule contribute to different aspects of the decision-making process in behavior generation. While the dorsal ACC plays a role in external choices and a cognitive decision to act, the inferior parietal lobule plays a role in selecting the effectors of an action, and making internally driven movement choices. In line with this view, Goldberg et al., (2008) suggested that the inferior parietal lobule is able to generate behavior by using cues from the internal environment for making choices. Taken together, the dorsal ACC functions to determine whether the action will be performed, whereas inferior parietal lobule supports planning and execution of internally driven actions by selecting the effectors of the action.

The above findings can be integrated to provide a neurocognitive framework of goal-directed behavior (Fig. 3). In this framework, internal or external stimuli are evaluated for their hedonic or reward value, which are expected to be processed in the ventral ACC (reward-based learning) and posterior cingulate cortex (autobiographical memory). Sufficient reward potential from an action may lead to the intention to act, which activates the lateral parietal cortex to form an action plan. Our model shows that goal-directed action has two components – a traditional component of goal-selecting and choosing an action plan that is externally-oriented and occurs in the dorsal ACC and lateral prefrontal cortex, and a novel component of internally-oriented selection of the effectors of action and initiating the action. To elaborate, the inferior parietal lobule in coordination with the dorsolateral prefrontal cortex evaluates multiple action plans with the former selecting the plan of choice and the body movements needed (Beудel and de Jong, 2009), and the latter being involved in rule-learning, external goal representations, and monitoring performance (Riddenkoph et al., 2004).

In addition to the internal parietal lobule, higher-order motor control also involves the regulation of action execution, which is likely processed by the superior parietal lobule and intraparietal sulcus. These regions, along with the dorsal ACC, monitor external choices with the latter selecting the targets, and the former regulating action execution (Beудel and de Jong, 2009) as well as monitoring external outcomes (Botvinick et al., 2004). Execution of the necessary movement is regulated by control of attention and movement by the superior parietal lobule and intraparietal sulcus. Finally, a key aspect of volition is the perception of a causal relationship between the action performed and resulting changes in the external environment (sense of agency), which is mediated by the inferior parietal lobule (Chambon et al., 2015; Zwosta et al., 2015). The reward value of the outcome, in turn, is evaluated by the medial prefrontal cortex (Liu et al., 2011). Thus, the integration of segregated processes in the anterior and posterior as well medial and lateral cortical regions represent the transformation of self-related processes of goal formation and intention to directed motor movements.
It is important to note that the flow of information between these regions occurs in a parallel fashion and not sequentially, where activity in each region biases activity in all other regions (Cisek and Kalaska, 2010). In addition, we have focused on the role of cortical networks in goal-directed behavior, without considering the contribution of basal ganglia and thalamus to goal-directed behavior. The reason for this is that distinct networks of sub-regions in these latter regions have not been defined consistently and their functions are unclear, although deficits in subcortical structures are associated with relatively greater degree of apathy compared to those with primarily cortical deficits (Stuss et al., 2000).

7. Evaluating the role of the inferior parietal lobule in apathy

Understanding the neural basis of apathy rests on models of goal-directed behavior. In the previous section, we pointed out that cognitive models of goal-directed behavior include volitional processes such as intention, internally directed initiation of behavior, and sense of agency. We also described the neural basis for volitional processes in the context of goal-directed behavior, which was lacking in the current neural models. Based on this revised neural model of goal-directed behavior, the association between apathy and the lateral parietal cortex described in Section 2 can be explained as resulting from disruption of neural processes of internally-initiated action.

At present, symptoms of apathy are broadly classified into cognitive, affective, and motor subtypes based on deficits in specific neural substrates in the cortico-striato-thalamic circuits. The motor subtype has also been labelled as auto-activation deficit and was related to dopaminergic circuits linked to action initiation. However, in this case, action initiation does not differentiate between internally-initiated and stimulus-driven motor responses. Rather, the inhibitory input from the basal ganglia to the primary motor cortex is reduced. As this circuit forms a common pathway for all movements, the associated motor subtype of apathy shows a severe impairment in behavior generation. In contrast, we propose that apathy resulting from dysfunction of the inferior parietal lobule is associated with a reduction only in internally-initiated goal-directed behavior. That is, these patients are able to perform goal-oriented actions if asked to do so, but are unable to perform similar actions without the external stimulus to act. This form of ‘volitional apathy’ may be a subtype of deficient goal-directed behavior that is distinct from the subtypes currently described in the literature.

Taken together, we propose that patients with volitional apathy would show reduced internally-initiated behavior that results from a reduced capacity for internally-driven selection of effectors of movement, action initiation, and attribution of action outcomes to oneself due to deficits in the inferior parietal lobule. A key criteria for this subtype of apathy may be that patients need to be told what to do, and once such an external stimulus is present, the ability to execute actions remains relatively intact. The volitional subtype of apathy may not affect the neural processes of the ‘what-to-do’ aspect of goal-directed behavior but the ‘how-and-whether-to-execute’ aspect of it. The angular and supramarginal gyri are expected to be affected because these regions were most often associated with apathy (Sec. 3), direct electrical stimulation of these regions results in the urge to move and produces the sensation of movement in a somatotopically organized manner (Desmurget et al., 2009), and activity in this region increases when the choice of an effector to be made is made (Beudel and de Jong, 2009). The involved regions can be further anatomically specified, based on empirical studies in Section 3, to Area PF, PFr, PFM, and PFcm (Caspers et al., 2008; Eickhoff et al., 2005).

Several questions need to be answered in order to provide evidence-based support for this proposal. First, although the inferior parietal lobule among the parietal cortex regions is most often associated with apathy, it is not clear whether the proposed mechanism also operates in the surrounding regions, which have been implicated in a few studies. In the same vein, it is not clear whether apathy can result from a localized deficit within the inferior parietal lobule or whether lateralization plays a role. However, it should be noted that localized lesions in this region have not been reported to be associated with apathy, with the exception of a single case study, though the lesions were present in multiple locations besides the inferior parietal lobule (Siegel et al., 2014). Moreover, circumscribed lesions in the angular gyrus lead to various symptoms but not to apathy. Therefore, it may be argued that the association of this region with apathy is indirect. Also, current evidence does not indicate that either hemisphere is more often affected (Raimo et al., 2018). While this scenario is plausible, the generalized reduction in behavioral repertoire seen in apathy is more likely if the deficit occurs in the broader region due to its somatotopic distribution. The diffuse neural changes in neurodegenerative diseases, where apathy is most often linked to changes in the lateral parietal cortex, supports this interpretation. Furthermore, the slow pace of change in these diseases may lead to a gradual decline in neural input from this region for internally-directed action initiation.

Second, other functions of the parietal lobe such as attentional...
control, or deficits in the precuneus/posterior cingulate cortex can also be said to underlie the association with apathy. However, as apathy is primarily defined as a reduction in behavior, neural processes that underlie behavior generation are most likely to be affected. This may result in less self-initiated responses and increased reaction times on neuropsychological tests. In contrast, other functions such as executive functions may be relatively preserved.

Finally, the consensus criteria for the diagnosis of apathy requires that impairment be present in at least two of the three domains. This suggests that studies using these criteria are likely to find correlations in multiple regions (because impairment in different regions presumably underlie each domain). Moreover, neurodegenerative disorders, in which the association between apathy and the lateral parietal cortex is most often reported, affect widespread areas of the brain and patients often show comorbid neuropsychiatric symptoms. Apart from having distinct disease mechanisms, neurodegenerative diseases also progress at a gradual pace, which may allow for compensatory changes to take effect. For example, functional connectivity may be altered in the inferior parietal lobule and also in the DMN, FPCN, and salience network. Such widespread changes may affect behavioral performance, and disentangling their independent effects may be difficult. Furthermore, a number of studies do not find any association between apathy and an affected lateral parietal cortex and include studies that specifically investigated the neural correlates of distinct (and thus restricted) domains of apathy (Kumfor et al., 2018). In this complex picture where multiple domains of apathy are present in the setting of widespread neural changes, isolating the neural correlates specific to each subtype of apathy is challenging.

Keeping these challenges in mind, we suggest important factors to consider that may be especially relevant for investigating volitional apathy. First, items in existing questionnaires are suitable for the identification of volitional apathy. These items broadly assess whether patients are able to initiate actions and whether they need to be told what to do. Examples of the former are: 'Is getting started by oneself important to the patient' (AES), 'Lacks initiative’ (FrSBE, AES, LARS, AI), 'Puts little effort into anything’ (AES), 'Lack of spontaneity' (PANSS), 'Less likely to initiate a conversation' (NPI). An example of the latter is: 'Does things with reminders’ (FrSBe). This item suggests that a difficulty in initiating actions is solved when the choice of acting is made on behalf of the patient. The differentiation between behavioral apathy, which is most often associated with the basal ganglia, and volitional apathy may be that, in the latter case, patients are able to initiate behavior when asked to do so, whereas in the former case, the external stimulus does not evoke behavior. Thus, studies may consider looking at the relation between specific items in the questionnaires and neural changes.

Second, self-paced experiments that allow subjects to decide whether to respond can be expected to provide better neuropsychological and brain imaging results in case of volitional apathy because the absence of instructions to act in a specific manner may better approximate the specific symptom in these patients (needing to be told what to do). Tasks with instructions to act in a specific manner may render experimental conditions to not be voluntary or self-paced.

Third, changes in the inferior parietal lobule may make it more difficult to meet the threshold level of neural activity needed to initiate action. Thus, a parametric response may be envisioned where reduced neural activity in the region is associated with longer delays in action or fewer responses. It may also be possible to test whether strong inputs from, for example, the posterior cingulate cortex, are associated with stronger activity in the inferior parietal lobule, which crosses the threshold for initiating action. These plausible mechanisms can be tested with computational models similar to those used to investigate volitional actions (Douglas et al., 2015; Zhang et al., 2012).

Finally, the stage of the primary disease may be an important consideration. In several studies, apathy was associated with changes limited to the inferior parietal lobule and neighboring regions in early stages of AD (Guercio et al., 2015; Munro et al., 2015; Tumati et al., 2018). Given the complex syndromes often seen in these patients, progressive regional spread of pathology, and increasing severity of apathy, it may be possible that subtype-specific changes are masked. Similarly, other cognitive functions such as attention may also be impaired. Hence, these factors need to be considered in the study design.

8. Revised model of apathy and its evaluation

Our proposal also calls for reconsidering neural models of apathy. In Fig. 4, we incorporated the inferior parietal lobule along with other regions known to be affected in apathy, and highlighted the regional interactions that may be specifically involved in initiating actions.

The regions implicated in apathy form a chain of processes that lead to the generation of intentional behavior. Affective apathy is most often associated with changes in the ventral ACC and medial prefrontal cortex where neural processes related to reward evaluation are localized. Cognitive apathy is most often associated with the dorsal ACC and lateral prefrontal cortex, where neural processes of goal selection and action inhibition are localized. The proposed subtype of volitional apathy is related to the internally-oriented processes for determining the effectors of action and evaluating the outcome of action, which are localized to the inferior parietal lobule. Lastly, behavioral apathy is associated with deficits in the basal ganglia that acts as the final gateway to action execution, and its dysfunction leads to a marked reduction in behavior. The inferior parietal lobule participates in the
internally-oriented DMN and externally-oriented PFCN, dorsal attention network, and salience network, which may facilitate the transformation of internal states to goal-directed action. This process may be deficient in the volitional subtype of apathy. By recognizing the role of the inferior parietal lobule in participating in internally- and externally-oriented functional networks, a network framework is identified to explore the basis for the involvement of other regions such as the precuneus in apathy that are reported in some studies. While further studies are needed to evaluate the proposed mechanisms, the revised model can be used to better understand apathy symptoms in patients.

Recent studies have advocated the use of dimensional scales in assessing apathy in amyotrophic lateral sclerosis and traumatic brain injury patients (Arnould et al., 2013; Radakovic and Abrahams, 2014). One such instrument proposed is the Dimensional Apathy Scale, which is designed to assess three subtypes of apathy – cognitive/behavioral initiation, emotional, and executive variants (Radakovic and Abrahams, 2014). Similar approaches (e.g. (Aleman, 2014)) may provide insights into reduced behavior and help to identify associated neural deficits. Current approaches for assessing apathy are based on aggregating symptom clusters, which are also used to assess the neural correlates of apathy. Only a few studies have directly investigated the neural correlates of subtypes of apathy (Benoit et al., 2004; Kumfor et al., 2018). Moreover, it has been suggested that the neural basis of apathy differs across disorders (Fernández-Matarrubia et al., 2018; Huey et al., 2017; Stanton et al., 2013), and that even its clinical presentation may differ in different disorders (Fernández-Matarrubia et al., 2018). Although these studies did not report changes associated with the lateral parietal cortex, their findings underscore the need for further studies taking into account specific clinical features of this complex syndrome. Further research is needed to validate the neurocognitive mechanisms of subtypes of apathy in general, which calls for different symptom assessment and neuropsychological testing.

9. Conclusion

To summarize, we evaluated the association between apathy and the lateral parietal cortex in the extant literature, and provided an analysis of the underlying neurocognitive mechanisms. The lateral parietal cortex by itself, rather than the prefrontal cortex, selects the action programs in the pursuit of set goals. This is achieved through the selection of effectors and facilitated by the dynamic maintenance of body schema in this region. Specifically, the inferior parietal lobule is spatially embedded within the broader lateral parietal cortex that serves goal-directed action control, and particularly the intermediate region between the angular and supramarginal gyri function to initiate specific effectors through the motor cortex. This region, through its functional participation in internally-oriented and externally-oriented networks, enables the transformation of internal states (needs or wants) to externally-oriented actions. The inferior parietal lobule also functions to generate the sense of agency through feedback processes matching the perception of the intention to act with actual movement, which strengthens the role of this region in self-intended behavior. The disturbance of these functions is the likely basis for its association with apathy. The weakening of neural input from this region may impair the initiation of intentional goal-directed actions. The specific symptoms of this subtype are likely to be difficulty in initiating behavior and needing instructions to perform routine or habitual actions. The proposed mechanism for these symptoms is a weakening in the neural process of initiating intentional behavior, which either require a stronger input from internally-oriented processes or an external impulse (such as being told what to do). On this basis, we propose that deficits in the inferior parietal lobule lead to a distinct subtype of apathy that we term as volitional apathy.

In conclusion, reports of the association between apathy and the lateral parietal cortex have not received sufficient attention in the literature. Efforts in this direction may yield a better understanding of the neurocognitive basis of apathy and aid in the search for treatments. Future studies can utilize the proposed models to directly investigate whether deficits in internally-driven action initiation by the inferior parietal lobule are associated with a general difficulty in selecting a specific action outflow channel or effector. Given the associations of the lateral parietal cortex with apathy across various disorders, its mechanisms deserve to be studied in more detail.

Acknowledgment

AA was supported by a consolidator Grant from the European Research Council (ERC), grant no. 312787.

References


Tumati et al. Progress in Neurobiology 175 (2019) 20–34