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Study of the temporal deployment of attention: Identification and characterization of psychological, neural and physiological indicators of mental effort.

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The temporal deployment of attention: Identification and characterization of psychological, neural and physiological indicators of mental effort.

ABSTRACT

The main objective of this thesis is to show that attentional reinforcement induced by an intensive short session of mental training (MT), induces a temporal deployment of attention and optimize temporal preparation. The second objective is to show that when the mental effort is maintained for a long time, it may lead to mental fatigue. We try to find psychological, neurological and physiological markers of mental effort for a better characterization of the mental fatigue described in everyday life and neurological diseases. In the first study, we showed that MT optimized temporal expectancies for shortest foreperiods "FPs" (250/280ms in intrinsic alertness and 650ms in extrinsic task). Strengthened effective connectivity between the right anterior insula (AI) and anterior cingulate (ACC), AI and dorsolateral prefrontal cortex (DLPFC) during intrinsic alertness and between the DLPFC and ACC, during extrinsic alertness was observed. The second study showed after MT, increased reaction times by the end of the session only in intrinsic alertness (250/280ms FPs) associated with decreased connectivity between AI-ACC and AI-DLPFC. We suggest that FP and MT may play a crucial role in temporal deployment of attention and would constitute psychological and neurological markers of mental effort or fatigue, notably through AI-ACC-DLPFC network. In the third study, we examined the relation between a physiological component "cortisol" and mental effort. Preliminary results show that the motor imagery task was more demanding in terms of cortisol secretion and was related to increase of hypothalamus and brainstem activity. This study shows that hypothalamus and brainstem may play a major role in the regulation of cortisol secretion in response to cognitively demanding situation.

Key words: Alertness, Mental effort, Temporal attention, Foreperiods, fMRI, Effective connectivity.

Etude du déploiement temporel de l'attention: identification et caractérisation d'indicateurs psychologiques, physiologiques et neuronaux de l'effort mental

Résumé

L'objectif principal de cette thèse est de montrer que l'entrainement mental (EM) induit par imagerie motrice entraine un déploiement temporel de l'attention et optimise la préparation temporelle. Le deuxième objectif est de montrer que lorsque l'effort mental est maintenu durant une longue période, il peut entraîner une fatigue mentale. Nous essayons de trouver des marqueurs psychologiques, neurologiques et physiologiques de l'effort mental pour mieux caractériser la fatigue mentale. Dans la première étude, nous avons montré que l'entraînement mental optimisait les attentes temporelles pour les courts foreperiods « FP » avec un renforcement de la connectivité effective entre l'insula antérieure (AI) et le cortex cingulaire antérieur (ACC), l'AI et le cortex préfrontal dorsolatéral (DLPFC) (FP = 250/280ms: alerte intrinsèque) et entre le DLPFC et l'ACC (FP=650ms : alerte extrinsèque). La deuxième étude a montré après l'imagerie motrice, une augmentation des temps de réaction vers la fin de la tâche pour l'alerte intrinsèque (FP=250/280 ms) avec une diminution de la connectivité entre AI-ACC et AI-DLPFC. Nous suggérons que la FP et l'EM pourraient jouer un rôle dans le déploiement temporel de l'attention et constitueraient des marqueurs psychologiques et neurologiques de l'effort mental via le réseau AI-ACC-DLPFC. Dans la troisième étude, nous avons examiné la relation entre l'effort mental et une composante physiologique «cortisol». Les résultats ont montré que la concentration de cortisol était élevée au niveau de la tâche d'imagerie et était liée à l'augmentation de l'activité de l'hypothalamus et du tronc cérébral. Cette étude montre que ces régions pourraient jouer un rôle dans la régulation de la sécrétion de cortisol en réponse à une situation cognitivement exigeante

Mots-clés: Alerte, effort mental, attention temporelle, Foreperiod, IRMf, connectivité effective.

Etude du déploiement temporel de l'attention: identification et caractérisation d'indicateurs psychologiques, physiologiques et neuronaux de l'effort mental

Résumé

L'attention est considérée comme la fonction cognitive la plus étudiée dans le domaine de la psychologie et des neurosciences comportementales.(Sarter, Givens, & Bruno, 2001)(Corbetta & Shulman, 2002; Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011; W. Sturm et al., 2006) Il s'agit d'une faculté que nous utilisons couramment dans notre vie quotidienne et que nous adaptons en fonction de notre environnement et de nos réalisations. Les théories en neurosciences cognitives décrivent l'attention comme un processus multi-système comportant de nombreux aspects (Parasuraman, 2000; Petersen et Posner, 2012; Posner et Petersen, 1990; Humphreys et Riddoch, 1993). Il semblerait que la capacité d'ajuster et de maintenir son attention au cours du temps serait évolutionnaire et adaptatif. (Posner (1971)) a défini l'alerte, la mémoire sélective et l'orientation de l'attention comme étant des composantes de base de l'attention. Ces composantes ont été différemment étudiées dans la littérature (vigilance, attention soutenue, attention spatiale, etc) (Corbetta & Shulman, 2002; J T Coull & Nobre, 1998; W. Sturm et al., 2006; Walter Sturm et al., 2004). Cependant, certains autres aspects fondamentaux de l'attention tout aussi importants, notamment le maintien de l'attention au cours du temps, les effets de l'attention (concentration) sur des intervalles de temps courts ou la perception temporelle de l'attention restent encore des concepts relativement mal compris et peu explorés. Nous proposons dans ce travail de thèse d'examiner et d'étayer ces concepts théoriques en proposant une démarche expérimentale et un cadre explicatif des mécanismes comportementaux et neuronaux explorés en imagerie fonctionnelle IRMf.

L'attention est distribuée dans l'espace et dans le temps. Elle contient donc deux grandes dimensions : une dimension spatiale et une dimension temporelle (Jennifer T. Coull, 2004). Dans notre vie de tous les jours, quand un évènement saillant survient, notre attention est rapidement dirigée vers l'évènement en question. Les informations capturées spatialement et

temporellement permettent d'optimiser et d'adapter notre comportement. Prenons ainsi l'exemple d'un feu tricolore à l'intersection d'une rue ; il semblerait que nos temps de réaction soient plus rapides si nos ressources attentionnelles sont mobilisées au moment où nous nous attendons à ce que la lumière passe du rouge au vert. Si la couleur du feu tricolore change plus tôt ou plus tard que prédit, nos réactions seront soit retardées, soit optimisées puisque la probabilité d'occurrence augmentera avec le temps.

La notion de temps revêt différents aspects et différentes formes. Alors que dans la théorie de la relativité restreinte et générale (physique fondamentale) le temps n'existe pas, dans la cinématique Newtonienne (physique classique), la notion de temps existe et permet de caractériser le mouvement ou le déplacement d'un objet dans l'espace. Paradoxalement, Albert Einstein définissait le temps comme une durée « propre » à chacun, à chaque objet, à chaque chose en fonction de sa position dans l'espace mais ce temps n'est ni commun, ni partageable entre les objets et les individus. Gaston Bachelard, philosophe et épistémo logue, évoque le temps comme une réalité, celle de l'instant. Autrement dit, le temps est une réalité resserrée sur l'instant et suspendue entre deux néants. Dans les études en psychologie cognitive, l'écoulement du temps est perçu sous forme de flow et relèverait de processus inconscients guère scientifiquement démontrés.

D'un point de vue neuroscientifique, la perception et le passage du temps peuvent être approchés en manipulant la concentration et les composantes de l'attention sensibles à l'écoulement du temps comme par exemple l'alerte dans notre étude. Ainsi, diverses expériences, utilisant des tâches de temps de réaction visuelles ou auditives, ont été menées pour étudier les traitements temporel et cognitif de l'attention. Les auteurs postulent que les participants sont plus rapides lorsqu'il leur est demandé de détecter une cible précédée d'un signal informatif ou signal avertisseur (Christina Nobre, 2001; Niemi & Näätänen, 1981; Périn, Godefroy, Fall, & de Marco, 2010; Walter Sturm & Willmes, 2001). En effet, lorsqu'un stimulus avertisseur est présenté quelques centaines de millisecondes avant la cible (stimulus impératif), le sujet se prépare temporellement à répondre plus efficacement à l'arrivée de la cible. Cependant lors des tâches de détection simple, les participants ne disposant d'aucune information sur l'apparition de la cible, l'attention serait implicitement dirigée vers celle-ci. Nous évoquerons deux théories distinctes de l'attention: l'attention dirigée vers un but et l'attention dirigée par un stimulus (Egeth & Yantis, 1997). La différence entre ces deux types d'attention est que la première implique des attentes temporelles volontairement guidées en fonction des indices et des instructions (attention dirigée vers un objectif) (Barnes & Jones,

2000; Michael I. Posner, Snyder, & Davidson, 1980), alors que la seconde implique une attention involontaire et rapide, dépourvue d'indices temporels explicites.

Les notions de temps et de durée et sont donc intrinsèquement liés aux processus attentionnels. Ensemble, ils traduisent des processus dynamique et fluctuant (Jennifer T. Coull, 2004). Le temps considéré comme vecteur de l'information (Scott W.Brown 2008) devient une caractéristique ou un indicateur fondamental du stimulus en cours ou à venir. L'arrivée d'un stimulus et le moment critique de son occurence pourraient constituer des déterminants de la performance Cognitive. Afin d'exprimer des décisions cohérentes, (quand et comment réagir), le sujet doit générer des stratégies temporelles permettant de réagir au moment le plus approprié. Ainsi, les paramètres de temps et de durée conditionnent l'efficacité de traitement des informations cognitives et des actions motrices à mener.

L'objectif de ce travail de thèse est donc de tenter de décrire les mécanismes psychologiques et neurophysiologiques qui sous-tendent les caractéristiques temporelles de l'attention permettant le traitement rapide de l'information et de faciliter le déploiement temporel de l'attention en optimisant les conditions expérimentales de l'étude (imagerie mentale) Une méthode d'analyse des indicateurs psychologiques, et neuronaux sera décrite et permettra d'appréhender les processus et les troubles de l'attention présents dans de nombreuses pathologies telles que sclérose en plaques, la fatigue chronique ou encore la fatigue à l'école ou au travail.

Dans ce travail, l'alerte a été choisie comme composante attentionnelle bien adaptée pour étudier les hypothèses qui concernent les aspects temporels de l'attention. L'alerte peut-être subdivisée en deux sous-composantes : l'alerte intrinsèque, endogène ou tonique et l'alerte extrinsèque, exogène ou phasique. L'alerte intrinsèque est très souvent reliée dans la littérature à l'attention soutenue, à la vigilance ou arousal (Oken, Salinsky, & Elsas, 2006a). En d'autres termes, des changements ou une modulation du niveau de la vigilance sont susceptibles de produire des fluctuations dans le traitement temporel de l'information. L'alerte intrinsèque définit également le degré d'éveil nécessaire pour effectuer une tâche de la vie quotidienne qui peut changer en quelques secondes, quelques minutes en fonction de facteurs psychologiques tels que le stress, l'anxiété, l'anticipation et de facteurs physiologiques tels que le rythme circadien, le cycle veille-sommeil (Jeannerod, 1995). L'alerte extrinsèque fait référence à la capacité de réagir à court terme après un signal avertisseur qui pourrait être présenté dans la même modalité sensorielle ou dans une autre modalité différente de celle du

stimulus impératif (Périn et al., 2010; Sarter et al., 2001; W. Sturm et al., 1999). Le stimulus avertisseur est utilisé pour informer du moment d'apparition de la cible contrairement à l'alerte intrinsèque, dans laquelle les sujets ne disposent d'aucune information explicite sur l'apparition de la cible.

Le processus d'alerte est souvent étudié avec des tâches de temps de réaction (TR). Un paradigme typique de TR simple, malgré sa simplicité, comprend de nombreux paramètres qui peuvent être changés d'une tâche à l'autre: le signal avertisseur (SA), le stimulus de réponse ou appelé également stimulus impératif (SI), la réponse elle-même (R) ou le temps de réaction (TR), (Kia Nobre et al. 2010).

La préparation implicite dans le temps est une capacité cognitive complexe qui optimise les réponses comportementales lors de l'apparition d'une cible après un certain intervalle de temps, nommé FP (foreperiod). La préparation implicite peut être abordée à l'aide de l'alerte intrinsèque. Plusieurs travaux ont montré qu'au cours d'une tâche de TR simple avec des FPs de durées variables apparaissant aléatoirement et de manière équiprobable, les TRs étaient plus courts pour des FP longs (Capizzi, Correa, Wojtowicz, & Rafal, 2015; Jennifer T. Coull, 2009; Niemi & Näätänen, 1981). En outre, les réponses étaient plus lentes lorsque le FP précédent était plus long que le FP en cours. Les auteurs de ces études parlent d'effets séquentiels et asymétriques du FP dépendant de la durée des FP qui précède la réponse en cours (Drazin, 1961; Los & Van Den Heuvel, 2001; Steinborn, Rolke, Bratzke, & Ulrich, 2008; Vallesi & Shallice, 2007; Woodrow, 1914). Dans l'alerte extrinsèque, FP représente la période qui s'écoule entre (SA) et (SI) pendant laquelle le sujet se prépare à répondre. La capacité de réagir rapidement et de prédire le moment exact de l'apparition du stimulus impératif au cours de cet intervalle nécessite un niveau élevé de vigilance (arousal) et de traitement temporel de l'information qui implique à son tour des stratégies d'anticipation et de raisonnement. FP inclut des paramètres psychophysiques tels que sa durée et sa distribution dans la tâche (FP variable). Ces paramètres peuvent affecter directement le traitement temporel de l'information et par conséquent la performance de la réponse motrice (R) ou plus explicitement le TR.

Il existe de nombreux débats dans la littérature concernant les différents processus influençant le phénomène de préparation temporelle et les effets de la durée des FPs. Il ressort de cette littérature une dissociation fonctionnelle de la préparation temporelle implicite avec un effet FP relié à un mécanisme contrôlé et préparatoire consommant des ressources et des effets séquentiels qui soutiendraient des mécanismes plus automatiques. Quoiqu'il en soit, la

préparation implicite sur le temps s'intègrerait dans un continuum contrôlé-automatique des processus cognitifs.

Dans ce contexte théorique, ce travail de thèse porte sur l'étude des interactions cognitivo-comportementales d'une tâche d'alerte en tant que composante fondamentale de l'attention et en utilisant FP comme indicateur psychophysique permettant d'examiner les différentes étapes du traitement temporel de l'information. Au cours de ce travail de thèse, nous avons cherché à déterminer des marqueurs psychologiques, neurologiques et physiologiques de l'effort mental qui devraient permettre de mieux caractériser et définir la fatigue mentale décrite dans la vie de tous les jours, dans l'éducation, le sport et les maladies neurologiques telles que les maladies chroniques. L'originalité de ce travail de thèse réside dans le fait que nous avons utilisé des approches qui émanent de la psychologie, du comportement, de la physiologie et de la neuro-imagerie fonctionnelle (IRMf). La démarche méthodologique proposée permet d'étudier des fluctuations temporelles des FPs sur de très courts laps de temps (< 1 seconde) auxquels le comportement (TRs), le système nerveux autonome et l'activité cérébrale devraient être sensibles.

Ainsi, trois études expérimentales ont été menées.

L'objectif principal de la première étude était de montrer que le renforcement de l'attention induit par une session courte et intensive d'imagerie motrice entrainait un déploiement temporel de l'attention et permettait d'optimiser la pression temporelle en maintenant un niveau élevé d'arousal pour améliorer la préparation temporelle. Nous avons manipulé le processus d'alerte et optimisé la préparation temporelle en utilisant une tâche d'imagerie motrice (15 minutes) en tant qu'entrainement mental. Nous avons utilisé un paradigme dans lequel les durées FPs variaient sur une échelle de temps allant de 250ms à 710ms. Ces FPs étaient distribués aléatoirement sur huit blocs d'essais suivant un design bloc à FP variables.

L'objectif de la deuxième étude était de montrer que lorsque l'effort mental était maintenu pendant une longue période, l'attention soutenue diminuait au cours du temps et pouvait entraîner une fatigue mentale, impactant les processus temporels de l'attention sur le plan comportemental et neural.

La mise en œuvre d'un protocole combinant à la fois une tâche d'alerte cognitivo-motrice et une tâche d'imagerie motrice nous a permis de mettre en évidence les régions cérébrales impliquées dans le traitement temporel de l'information et de proposer un modèle neural du déploiement temporel de l'attention au sein d'une population de sujets sains.

Ce modèle neural putatif était composé de trois régions de l'hémisphère droit: le cortex préfrontal dorsolatéral (DLPFC), le cortex cingulaire antérieur (ACC) et l'insula antérieure (IA). Le DLPFC et l'ACC sont connus pour être impliqués dans des tâches cognitives et notamment dans le contrôle et le maintien de l'alerte (Clemens et al., 2011, 2013; Périn et al., 2010; Walter Sturm & Willmes, 2001). En outre, des études récentes ont montré que l'AI pouvait aussi constitué une composante importante de l'alerte, en particulier l'alerte intrinsèque (Coste & Kleinschmidt, 2016; Sadaghiani & D'Esposito, 2015). Nous supposons dans notre modèle neural que l'AI générerait un control bottom-up nécessaire au maintien de l'alerte. De plus, nous spéculons que ces trois régions partageant une architecture neuronale spécifique composée d'une proportion de neurones fusiformes munis d'un axone de grande taille avec peu de dendrites, nommés neurones Von Economo (VENs), pourraient être sollicités pour accroitre la vitesse de transfert de l'information. La contribution des VENs au plan neural et comportemental reste encore flou. Ils sont connus pour intervenir chez l'homme dans la prise de décision « sociale » et dans l'intuition (Allman, Watson, Tetreault, & Hakeem, 2005). On les retrouverait également dans certaines espèces animales (dauphin, grand singes). Dans notre étude, nous spéculons qu'ils pourraient faciliter le transfert d'information.

La thèse est divisée en trois parties et Les hypothèses suivantes ont été examinées:

1- La tâche d'imagerie motrice utilisée intensivement avant la réalisation de la tâche motrice réelle pourrait améliorer la performance cognitive en augmentant le niveau d'arousal et en diminuant les (TRs), en particulier aux intervalles FP les plus courts, notamment en utilisant la tâche d'alerte intrinsèque.

2- De nombreuses études ont montré que l'arousal, lié au système nerveux autonome, serait contrôlé par des stimulations provenant des afférences noradrénergiques et cholinergiques que l'on retrouve au niveau du tronc cérébral (Jones, 2003), Clemens et al., 2011; Gaspar, Berger, Febvret, Vigny, & Henry, 1989). Ces mêmes études ont prouvé que l'arousal serait une fonction prise en charge par l'hémisphère droit cérébral (Langner & Eickhoff, 2013(W. Sturm et al., 1999)) et pourrait s'identifier par un réseau fronto-pariétal étendu qui interviendrait dans le contrôle de l'arousal. L'hémisphère droit serait principalement impliqué dans l'activation des voies sympathiques qui changerait d'une manière automatique et involontaire en fonction des changements homéostatiques du milieu pour répondre à des stimuli inattendus et aux comportements urgents (Craig, 2005; Rogers & Andrew, 2002; Wittling, 1995).; Jones, 2003; Robinson et Coyle, 1980).

En nous appuyant sur des hypothèses de la littérature et des résultats obtenus dans la partie comportementale de notre étude, nous proposons un modèle neural de l'alerte sensible au processus attentionnels qui faciliterait le traitement temporel et rapide de l'information. Nous suggérons une activité synaptique renforcée dans l'hémisphère droit des régions AI, ACC et DLPFC connues pour leur implication dans les processus d'alerte et nous examinons la connectivité effective des circuits AI-ACC et AI-DLPFC dans le cas de l'alerte intrinsèque et DLPFC-ACC dans le cas de l'alerte extrinsèque, notamment aux FPs de courte durée qui optimiseraient les effets de l'arousal. 3- Nous supposerons également qu'à l'issu de 30 minutes de tâche (imagerie motrice + tâche physique réelle), les ressources attentionnelles des participants pourraient diminuer, se traduisant sur le plan comportemental par une augmentation des TRs. La diminution des ressources attentionnelles, pourrait traduire les efforts mentaux produits par les participants et sera perçu comme une fatigue mentale qui sera majorée au cours de la tâche intrinsèque du fait d'une sollicitation importante de l'état d'éveil et vigilance. Cet état d'éveil diminué devrait se répercuter au niveau des processus du traitement temporel de l'information qui sera associée à une diminution de la connectivité effective au niveau des circuits endogènes AI-ACC et AI-DLPFC en particulier aux FPs les plus courts.

Dans la troisième étude, nous avons examiné la relation entre l'effort mental et l'activité du cortisol qui pourrait constituer un marqueur naturel et physiologique de la fatigue mentale. En effet, le cortisol représentant un corticostéroïde surrénalien, représente une hormone qui interviendrait lors de situation de stress ou de fatigue chez l'homme. Elle serait libérée suite à une augmentation de l'arousal et lors d'une activation de l'axe surrénalien-hypothalamo-hypophysaire- (HPA) (Lupien, Maheu, Tu, Fiocco et Schramek, 2007; McEwen, 1998). Cette molécule a été aussi associée dans nombreuses études cliniques tels que le syndrome stress post-traumatique, le syndrome de fatigue chronique et la fibromyalgie, (A. D. L. Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004) (Werbel et Ober, 1993) à de la fatigue qui serait un symptôme commun lié à une réduction des taux de cortisol (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Nater et al., 2008). Dans le cerveau, la régulation de la sécrétion de cortisol est assurée par différentes structures neuronales en fonction de la nature des facteurs de stress (physiques ou psychologiques).

Diverses études en neuroimagerie sur les changements de l'activité cérébrale en réponse au stress, suggèrent une contribution du tronc cérébral dans le stress physique, tandis que les facteurs de stress psychologiques ont tendance à engager des régions du système limbique telles que l'hippocampe (HC), l'amygdale (AG) et le cortex préfrontal (PFC) inclut dans notre modèle neural (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009).

Dans ce contexte, en complément des régions déjà modélisées dans notre étude, nous avons exploré d'autres régions comme l'hypothalamus et le tronc cérébral qui interviendraient dans la régulation de l'arousal. Nous avons émis l'hypothèse suivante : La tâche d'imagerie motrice qui sollicite des niveaux importants d'arousal pourrait entrainer un stress, qui augmenterait potentiellement le niveau de cortisol et favoriserait donc une activité accrue de l'HPA.

Afin de pouvoir examiner toutes ces hypothèses, nous avons mis en place un protocole dans lequel on a intégré deux taches d'alerte (intrinsèque et extrinsèque). Trente-neuf participants en bonne santé (20 femmes et 19 hommes), droitiers et âgés de 21 à 35 ans (moyenne = 27,5; ds = 4,50) sans antécédents connus de troubles neurologiques, psychiatriques ou sensorimoteurs ont été recrutés pour exécuter une tâche cognitivo-motrice en IRMf. Ils ont été priés de concentrer leur attention et de presser une poignée avec la main gauche aussi rapidement que possible lorsqu'une cible apparaissait (carré blanc) en respectant le niveau de force requis (faible, moyen et élevé). L'utilisation de la main gauche avait pour but d'inciter les participants à produire plus d'effort mental pendant l'entraînement mental. Les trois niveaux de forces étaient choisis principalement pour, obliger les participants à être en alerte,

préparer leur geste sans produire de réponses réflexes (automatiques), et à rester concentré sur toute la durée de la tâche. Le paradigme comportemental était construit selon un design en bloc avec des FPs variables randomisés et répartis aléatoirement sur huit blocs d'essais.

La durée des FPs variait entre 250, 280 et 310 ms pour la tâche intrinsèque et entre 650, 680 et 710ms pour la tâche extrinsèque. Une tâche de contrôle sensorimoteur a été utilisée dans laquelle les participants pressaient la poignée à une fréquence d'environ (1 Hz) tout en observant passivement un carré blanc clignotant rapidement (10 Hz). Les systèmes d'alerte n'étaient pas sollicités.

La moitié des participants ont réalisé la tâche d'imagerie motrice, avant de réaliser la tâche physique réelle (groupe mental «grM » (n=19)). Les sujets étaient priés d'exécuter exactement la même tâche mais mentalement en imaginant presser la poignée (sans sortie motrice).

Les deux tâches duraient 30 minutes (2 x 15 minutes). Le groupe mental «grM » a été comparé au groupe physique « grP » (n=20).). Des échantillons de salive ont été prélevés deux fois : au début du run (échantillon 1 «S1») et à la fin du run (mental ou physique) (échantillon 2 «S2») chez 13 participants. Six participants avaient débuté avec la tâche mentale et 7 autres participants avaient débuté avec la tâche physique. Chaque échantillon a été analysé. Les données ont été conservées de manière sécurisée et codées pour assurer l'anonymat des participants.

Les deux groupes ont subi une batterie de tests neuropsychologiques comprenant trois tests sélectionnés en fonction de leur domaine cognitif. Le d2 qui permettait de mesurer les capacités de concentration et de vitesse des particpants (attention soutenue et balayage visuel respectivement)(Bates & Lemay, 2004). Le test de Stroop qui mesurait les fonctions exécutives, l'attention sélective et l'inhibition cognitive (Golden, 1976) et finalement Le trial making test «TMT» (parties A et B) qui fournissait des informations sur la recherche visuelle, le balayage et la flexibilité mentale (Pena-Casanova et al., 2009; Tombaugh, 2004). Tous les participants avaient passé les tests avant l'entrée dans l'IRM et après leur sortie. Un test de perception d'effort « RPE » a également été réalisé après IRM. L'échelle RPE permet de connaitre l'effort perçu ressenti au cours de la tâche (Borg & Dahlström, 1962). Autrement dit, ce test permettait aux participants d'exprimer une intensité subjective d'effort, de tension ou d'inconfort, en fonction de la tâche accomplie. Les scores issus de ces tests étaient statistiquement comparés en intra et en inter groupes (imagerie« grM » versus sans imagerie « grP »).

Sur le plan comportemental, les temps de réaction (RT) étaient extraits pour les deux tâches d'alerte (intrinsèque et phasique) à l'aide des logiciels Acknowledge (version 4.2) et E-prime (version 2.0.8.22). Les TRs qui étaient supérieurs à 1000 ms ou inférieurs à 100 ms ont été exclus de l'analyse. L'analyse statistique a été réalisée avec le logiciel Statistica® (version 13.3) et le seuil de signification a été défini à $p < 0,05$.

Sur le plan imagerie, le prétraitement des images a été effectué à l'aide du logiciel SPM12 (Statistical Parametric Mapping) (Centre de neuroimagerie humaine Wellcome, University College London, Royaume-Uni; http://www.fil.ion.ucl.ac.uk/spm). Les volumes EPI ont été corrigés pour tenir compte des différences de temps dans le volume et réalignés avec le premier volume pour corriger les mouvements de la tête. Les images fonctionnelles ont ensuite été co-enregistrées avec l'image 3D et normalisées spatialement par rapport à l'espace stéréotaxique standard du MNI. Un lissage spatial gaussien a été effectué sur les images en utilisant une largeur de fenêtre à mi-hauteur (FWHM)de 8 mm .

Les réponses hémodynamiques ont été modélisées en fonction de la réponse hémodynamique synthétique (HRF). Pour réduire au minimum la perturbation des données aux artefacts de mouvement, les vecteurs de mouvement dérivés du réalignement ont été intégrées dans le modèle linéaire général (GLM) en tant que régresseurs pour corriger le mouvement. Un modèle à effets fixes a été créé pour chaque participant et une analyse de groupe de second niveau prenant en compte les effets aléatoires a été entreprise.. Les résultats présentés en imagerie proviennent de l'acquisition d'images lors de l'exécution de la tâche physique réelle dont le seuil était corrigé (FWE) et fixé à $p < 0,05$.

Les résultats des tests neuropsychologiques ont montré que les performances cognitives étaient supérieures pour le groupe avec imagerie mentale « grM » (test stroop p=.005 et test d2 p=.009), pas de différence au niveau du (TMT). Pour le groupe mental, le test RPE révélait que la perception de l'effort était plus importante par rapport au groupe physique (p=.00003).

Une première analyse de la variance (ANOVA à deux facteurs) groupes ["grM" vs "grP"] x tâches [intrinsèque vs extrinsèque] a été réalisée pour examiner les effets de l'entraînement mental sur l'alerte.

Ensuite, une seconde analyse ANOVA a deux facteurs a été réalisée séparément au sein de de chaque tâche d'alerte pour tester les effets FPs [«650 vs 680 vs 710» pour la tâche extrinsèque et «250 vs 280 vs 310» pour la tâche intrinsèque] x groupes ["grM" vs "grP"] afin d'examiner les effets de l'entraînement mental sur les TRs. Lorsque l'ANOVA indiquait des effets et / ou des interactions significatives, des comparaisons post-hoc de Bonferroni étaient utilisées afin de corriger les erreurs de première espèce lors descomparaisons multiples.

Au niveau de l'alerte intrinsèque, les résultats de l'ANOVA [groupes x FPs] ont montré une interaction significative; F (2, 16) = 3,04, p = 0,04. Des comparaisons post-hoc ont montré, au sein du groupe «grP», des différences significatives de TR entre la FP = 250 ms (moyenne = 405,87 sd = 129,52) et FP = 310 ms (moyenne = 384,09, SD = 99,33) p=.001 et entre FP = 280 ms (moyenne = 402,64 SD = 117,77) et FP = 310 ms (moyenne = 384,09, SD = 99,33) p=.01. Aucune différence significative observée pour le « grM ».

En comparant chaque FP entre les groupes, les comparaisons post-hoc ont montré que les TR diminuaient significativement après l'entraînement mental, notamment pour FPs = 250 ms: « grM » (moyenne = 380,97, SD = 129,52) et «grP» (moyenne = 405,87, SD = 105,46) p=.008. Pour FP = 280ms: «grP» (moyenne = 402,64 sd = 117,77) et « grM » (moyenne = 374,15, sd = 89,85) p=.001. Aucune différence significative n'a été trouvée pour FP = 310 ms.

Au niveau de l'alerte extrinsèque, l'ANOVA [groupes x FPs] a révélé une interaction significative; (F (2, 14) = 3,1, p = 0,04). Les comparaisons post-hoc ont montré dans le groupe «grP», une différence significative de TR entre FP = 650 ms (moyenne = 415,37, SD = 140,25) et FP = 710 ms (moyenne = 393,66, SD = 131,60) p=.01. Aucune différence significative n'a été observée entre les FPs 680ms et 710 ms. Au sein du groupe « grM », aucune différence significative n'a été observée entre les trois FPs. Des comparaisons post hoc ont montré que les TRs diminuaient significativement après entraînement mental pour FP = 650ms «grP» (moyenne = 415,37, SD = 130,79) et « grM » (moyenne = 377,49, sd = 147,91) p=.001. Aucune différence significative n'a été retrouvée pour les FPs > 680 ms.

En imagerie, avec un paradigme quelque peu modifié, nous avons reproduit les résultats obtenus en 2010 dans Périn et al. avec l'alerte intrinsèque et extrinsèque. Dans une première analyse, tous les participants étaient regroupés (n = 39). Nous avons ensuite effectué une comparaison entre les groupes ["grM" > "grP"] en séparant l'alerte intrinsèque et extrinsèque pour investiguer les effets de l'entrainement mental sur ces deux types d'alerte et leurs effets sur la connectivité effective des circuits supposés. .

Une analyse d'interaction psychophysiologique (PPI) a été réalisée pour étudier les interactions entre AI, ACC et DLPFC afin de déterminer les effets de l'entraînement mental sur les circuits AI-ACC-DLPFC. L'analyse de connectivité effective permettait de tester l'hypothèse selon laquelle l'activité d'une région cible du cerveau pouvait s'expliquer par l'interaction entre la présence d'un processus cognitif (imagerie mentale) sur l'activité d'une région source. L'AI a été choisie comme région (source) dans la tâche intrinsèque puisqu'elle elle est sensible aux effets de l'arousal (contrôle bottom-up) et elle est richement interconnectée avec l'ACC et le DLPFC. Dans la tâche extrinsèque, DLPFC a été choisi comme région source exerçant un contrôle top-down sur l'ACC.

Les résultats d'imagerie ont montré pour « grM » > « grP », un renforcement significatif des activations dans l'hemisphère droit de l'AI, de l'ACC, du cortex pariétal inférieur (IPC), thalamus, cortex préfrontal dorsolatéral (DLPFC) et du Putamen dans les deux tâches d'alertes. Des activations bilatérales plus étendues dans l'hémisphère gauche de l'IPC et du putamen ont été observées au niveau de l'alerte extrinsèque.

Les résultats de connectivité effective ont montré pour l'alerte intrinsèque une augmentatio n significative de la connectivité entre AI (x: 39, y: 2, z: 10) et DLPFC (x: 51, y: 29, z: 31) pFWE = .001 et entre AI (39, y: 2, z: 10) et CCA (x: 9, y: 41, z: 7) pFWE = .01 pour FP = 250 ms et entre DLPFC (x: 57, y: 32, z: 19) et ACC (x: 3, y: 41, z: 7) pour la FP = 650 ms au niveau de l'alerte extrinsèque. PFWE =.005

Les résultats de cette étude ont montré, que l'effet FP était observable pendant les tâches d'alerte intrinsèque et extrinsèque, notamment dans le groupe sans entraînement mental « grP ». Les TRs diminuaient significativement aux FP longs (310ms pour l'alerte intrinsèque) et (710ms pour l'alerte extrinsèque), correspondant à l'effet FP classiquement décrit dans la littérature.

Suite à l'entraînement mental induit par l'imagerie motrice, les performances cognitives étaient améliorées dans les deux tâches d'alerte, principalement aux FPs les plus courts. Aucun changement de TR n'était observé lorsque la durée FP augmentait. Ainsi, l'effet FP semble disparaitre aux FP longs, La préparation temporelle serait optimisée aux FP courts. En effet, lors de la tâche d'imagerie motrice, les participants devaient s'imaginer répondre au stimulus impératif pendant une session courte et intensive de 15 minutes sans exécuter d'action motrice. On suppose que pendant cette période d'inhibition du mouvement moteur, le système nerveux autonome stimulé de façon permanente augmenterait le niveau d'arousal qui atteindrait un seuil élevé, facilitant ainsi l'encodage de l'information aux instants les plus

critiques (courts) de FPs. Ce résultat est en accord avec l'effet FP séquentiel de conditionnement et de traces mnésiques suggéré par Los et al. (2001). Ainsi, l'activation du SNA et le relâchement des processus d'inhibition (levée de l'inhibition) après imagerie mentale pourraient faciliter le déploiement temporel de l'attention. Ces résultats concordent avec les travaux de Kahneman (1973) qui considère que chaque stimulus susceptible de capter l'attention induit une augmentation soudaine et momentané du niveau d'arousal, notamment par des mécanismes non contrôlés et adaptatifs. Kahneman suppose aussi que l'arousal varie rapidement comme une réponse adaptative aux stimuli auxquels l'organisme est exposé. En comparaison avec les modèles de la littérature concernant les effets FP et les effets FP séquentiels, (Los & Van Den Heuvel, 2001) associe à chaque instant critique au cours d'une tache de TR une force de conditionnement développée au cours des essais, sorte de traces mnésiques de l'information temporelle.

Plus ce conditionnement est élevé à un instant critique, plus le TR sera raccourci si le stimulus impératif apparaît à ce moment propre. Il est raisonnable de supposer que l'entraînement mental augmente la «force de conditionnement» ou la mémoire des essais, augmentant par voie de conséquence les attentes temporelles de la réponse motrice. Ce résultat appuie le concept théorique de (Los & Van Den Heuvel, 2001) qui considère qu'après un entrainement, une réponse conditionnée se développe et ce d'autant que l'entrainement est intensif comme dans notre expérience, permettant d'atteindre un optimum au moment de l'arrivée de la cible (Gallistel & Gibbon, 2000; Grossberg & Merrill, 1992; Machado, 1997; S. Roberts, 1998).

En outre, (Vallesi & Shallice, 2007)) estiment dans leur modèle théorique de processus duel que l'état de préparation est globalement déterminé par le niveau d'arousal et considèrent que la force de conditionnement et le niveau d'arousal sont deux composantes interdépendantes du processus de préparation temporelle. Selon ce modèle, plus la force de conditionnement augmente, plus le niveau d'arousal sera important et aura tendance à augmenter pendant les délais courts des FPs. Nos résultats comportementaux vont bien dans le sens de la conceptualisation de ces modèles qu'ils permettent d'unifier en quelque sorte puisqu'ils résultent des composantes de chacun de ces modèles. Ainsi, une tâche d'imagerie motrice suivie d'une tâche motrice réelle facilite l'activation du SNA régulant les effets de l'arousal qui maintient un état optimum permettant de déployer l'attention sur une échelle de temps plus courte. En conclusion, l'imagerie mentale augmente l'arousal et la force de conditionnement entrainant une perception du temps accrue chez les participants les aidant à ajuster leurs attentes temporelles afin de traiter plus efficacement les informations au cours du temps.

Les résultats comportementaux ont été transposés au niveau neural en analysant la connectivité effective entre AI-DLPFC et entre AI-ACC (pour l'alerte intrinsèque) et DLPFC-ACC (pour alerte extrinsèque). Dans la littérature, il est démontré que l'IA fait partie intégrante du circuit de la régulation de l'alerte (Craig, 2002; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002). L'IA fournirait à l'ACC jouant le rôle de contrôle et de surveillance des informations temporelles qui transiteraient vers les régions corticales. L'IA jouerait ainsi un rôle crucial dans la perception et l'écoulement du temps. Elle utiliserait également des représentations des états du corps (Craig, 2009). Autrement dit, en intégrant temporellement les signaux successifs provenant du corps, IA coderait des «instants critiques» en lien avec la perception du temps et de la durée.

On pourrait supposer que, dans les tâches de temps de réaction avec des intervalles de FP variables, l'insula antérieure intègrerait des informations sur le temps écoulé (par période) après chaque stimulus qu'elle transfèrerait à l'ACC et au DLPFC. Ces informations seraient synchronisées sur des fenêtres temporelles (attentes) qui activeraient les représentations motrices pour produire le mouvement moteur (Langner, 2010). Le DLPFC, connu comme étant le socle de la préparation temporelle et de la mémoire de travail (Vallesi, Lozano, & Correa, 2013) maintiendrait les attentes d'apparition de la cible et guiderait le mouvement.

Il semble donc raisonnable de supposer que le traitement temporel de l'information pourrait transiter par un réseau cognitivo-moteur AI-ACC-DLPFC. Par conséquent, sur la base de ce modèle neural, nous suggérons que l'imagerie motrice et donc l'entraînement mental amélioreront les réponses motrices.

En nous basant sur les résultats comportementaux et d'imagerie, nous spéculons que les neurones von economo (VENs) présents principalement dans ces trois régions, pourraient jouer un rôle majeur dans le processus de traitement temporel de l'information. En effet, les VENs sont des neurones particuliers connus pour être impliqués fondamentalement dans l'intuition et l'adaptation rapide du comportement à des situations sociales changeantes (Allman et al., 2010, 2005). Dans ce travail de thèse, nous pensons qu'ils ne seraient pas seulement limités au domaine social. En effet, leurs caractéristiques morphologiques, leur grande taille, leur arborescence dendritique et le calibre des axones nous laissent penser que ces cellules qui émanent des voies pyramidales, se seraient modifiés au cours de l'évolution pour s'adapter à l'environnement et aux interactions sociales favorisant ainsi les échanges, notamment en conduisant plus rapidement les informations au niveau cérébral

Cette caractéristique morphologique devrait leur permettre de jouer un rôle critique dans le traitement temporel de l'information, de renforcer les temps de réaction (TR) et faciliter la prise de décisions (Allman et al., 2005). Sur la base des caractéristiques fondamentales des VENs, et puisqu'il est reconnu que ces neurones projettent massivement vers IA, ACC et DLPFC de l'hémisphère droit, nous spéculons qu'une adaptation rapide du comportement à des variations critiques du temps pourrait transiter au travers de ces neurones Néanmoins, d'autres investigations seront nécessaires pour confirmer cette hypothèse neurale.

Afin d'investiguer sur le plan comportemental les effets de l'effort mental prolongé sur le temps, une analyse de la variance ANOVA à mesures répétées entre groupes ["grM vs grP"] x blocs [premier vs dernier bloc] a été réalisée séparément au niveau de chaque tâche d'alerte, suivie d'une ANOVA à mesures répétées entre FPs [«650 vs 680 vs 710» pour l'alerte extrinsèque et «250 vs 280 contre 310» pour l'alerte intrinsèque] x blocs [premier vs dernier bloc] Afin d'examiner les effets de l'effort mental prolongé ou fatigue sur le traitement temporel de l'information.

Les résultats ANOVA à mesures répétées groups ["grM vs grP"] x blocs [premier vs dernier bloc] ont montré un effet significatif de l'effort mental dans le « grM » au niveau de la tâche d'alerte intrinsèque uniquement F (1, 1320) = 14,44 ; p=.00001.
Aucun effet significatif n'a été observé dans l'alerte extrinsèque et aucun effet significatif n'a été observé dans le « grP ».
Les comparaisons post-hoc ont montré des différences significatives de TR entre le premier et le dernier bloc ; premier bloc (moyenne= 401,61, sd = 130,83) et dernier bloc (moyenne= 440,14, sd = 149,02) P=.0001.

Au niveau de l'alerte intrinsèque, les résultats ANOVA à mesures répétées FPs [250 vs 280 vs 310ms] x [premier bloc vs dernier bloc] ont montré un effet significatif de l'effort mental sur les FPs, F (2 617) = 3,48. p= .03. Les comparaisons post-hoc ont montré des différences significatives de TR entre le premier et le dernier bloc au niveau des FPs les plus courts ; (FP= 250ms) premier bloc (moyenne= 403,17, sd = 137,22) et dernier bloc (moyenne = 466,63, sd = 161,36). P=.001 et FP = 280ms premier bloc (moyenne= 398,70, sd = 136,39) et dernier bloc (moyenne= 454,01, sd = 145,40). P=.004. Aucune différence significative n'a été observée pour FP = 310ms. En ce qui concerne l'alerte extrinsèque, aucun effet significatif n'a été démontré, quel que soit FP.

En imagerie, nous avons effectué une analyse univariée dans laquelle ont été comparés les TRs de début et de fin de bloc dans les deux groupes. Cette analyse avait pour but d'examiner les changements d'activité cérébrale des réseaux de l'attention au cours de l'alerte intrinsèque et extrinsèque en présence d'un effort mental prolongé, potentiellement de la fatigue. Ensuite, afin d'étudier les effets de l'effort mental prolongé sur les intervalles temporels FP, nous avons séparé les FPs et nous nous sommes appuyés sur une méthodologie similaire à l'étude précédente.

Sur le plan comportemental, les TRs avaient significativement augmenté entre le premier et le dernier bloc indiquant une baisse du niveau de l'arousal et très probablement un état de fatigue mentale s'installant progressivement principalement dans la tâche d'alerte intrinsèque. Les résultats d'imagerie ont montré qu'en comparant les blocs pour le groupe mental « grM », des diminutions d'activation (désactivations) significatives étaient observées dans la tâche intrinsèque dans le cingulum postérieur, DLPFC, gyrus frontal supérieur et médian (SFG / MeFG), IPC et du précuneus de l'hémisphère droit, régions appartenant au réseau en mode par défaut (DMN).

Au niveau de la tâche extrinsèque des activations significatives étaient retrouvées uniquement dans le DLPFC (BA 9/46), l'IA et le thalamus dans l'hémisphère gauche. Aucun changement d'activité significative n'a été observé dans le « grP ».

En séparant les FPs, les résultats ont montré des diminutions d'activité significatives dans les régions d'intérêt (AI, ACC et DLPFC) du déploiement temporel, i.e. aux FPs les plus courts (250/280 ms). Aussi, une diminution de la connectivité effective était démontrée entre les circuits AI et DLPFC et entre AI et ACC. L'alerte extrinsèque n'avait pas été explorée puisque qu'il n'y avait pas d'effet FP observé sur le plan comportemental.

L'imagerie motrice utilisée en tant qu'entraînement mental est intéressante pour permettre à l'attention de se déployer temporellement et accroitre les TRs. Néanmoins, son utilisation prolongée peut présenter des effets délétères et inversés. Sur le plan comportemental, les participants ont indiqué (à travers l'échelle RPE) que la tâche d'imagerie motrice demandait plus de concentration que la tâche physique, du fait probablement de devoir retenir la réponse motrice. Au cours de l'alerte extrinsèque, la présence du stimulus avertisseur pourrait avoir contribué au maintien de la performance. En effet,le stimulus avertisseur pourrait fournir une stimulation supplémentaire à l'arousal bénéfique pour le maintien de l'attention et de la

performance (Hackley et al., 2009). La demande cognitive de la tâche extrinsèque a conduit à recruter des régions de l'hémisphère gauche permettant au sujet de faire face aux demandes supplémentaires (processus explicites de sélection) de la tâche et de compenser le déficit normalement observé au niveau de l'alerte intrinsèque qui est connue comme étant une tâche monotone et qui nécessite beaucoup plus d'énergie et de ressources attentionnelles, ce qui la rend plus sensible à la fatigue mentale.

Ce résultat va dans le sens des résultats de (JT, RSJ, & CD, 1998) qui ont retrouvé des effets de fatigue exclusivement dans la tâche de détection simple et non dans la tâche sélective dans laquelle l'activité dans l'hémisphère droit était préservée tout au long de la tâche.

Au niveau de l'alerte intrinsèque, nous avons constaté une diminution de la connectivité effective entre AI-DLPFC et entre AI-ACC. En fait, le traitement des informations au niveau d'une tâche d'alerte intrinsèque implique un contrôle ascendant dans l'hémisphère droit, afin de faciliter la détection du stimulus et de préparer implicitement la réponse (Frith & Done, 1986; Goodrich, Kennard, & Henderson, 1989; Henderson & Dittrich, 1998). Ce contrôle bottom-up est généré par l'insula antérieure fortement liée à l'arousal qui fait à son tour partie du système nerveux autonome.

Ces modulations ascendantes sont les plus sensibles aux changements adaptatifs, potentiellement à la fatigue mentale qui pourrait affecter toutes les étapes du traitement de l'information de la détection du stimulus à l'exécution de la réponse.

Dans le cerveau, après effort mental et analyse de l'activité cérébrale, nous avons observé un déséquilibre de l'activité des différents réseaux. Classiquement, lorsqu'un stimulus extérieur se manifeste, l'activation du réseau en mode par défaut (default mode network - DMN) cesse et le réseau fronto-parietal (central executive network - CEN) prend le relai pour gérer le stimulus saillant. Les deux réseaux DMN et CEN sont supposés s'activer de manière anti-corrélée. Dans le cadre de notre protocole d'étude, ces deux réseaux étaient sollicités conjointement et simultanément, notamment après imagerie motrice. Nous avons observé une perte de désynchronisation entre le DMN et le CEN, probablement du fait d'une bascule permanente entre ces réseaux et d'une diminution de la stabilité de la dynamique des réseaux. L'effort mental ressenti pourrait être la conséquence de ces réseaux dynamiques instables. Aussi intéressant, l'insula antérieure et l'ACC qui constituent des région du réseau saillant (salient network - SN) interviennent dans la modulation de l'arousal (Menon and Uddin 2010)

et pourraient jouer un rôle important dans la régulation du DMN et du CEN. Dans notre étude, lorsque l'effort mental augmentait au cours du temps, une fatigue mentale semblait s'installer à la fin de la tâche (augmentation des TRs), l'activité du CEN (notamment DLPFC) diminuait et la désactivation du DMN (mPFC, PCC) s'accentuait. L'anti-corrélation de ces réseaux décroissait au cours du temps. Ainsi, nous pourrions attribuer la dérégulation des réseaux à une synchronisation partielle ou totale du DMN et du CEN mais elle reste à démontrer. Aussi, nous ne pouvons pas exclure la contribution de l'insula antérieure et/ou de l'ACC qui pourraient jouer un rôle de hub pour maintenir le déséquilibre des réseaux.

Lorsque la fatigue s'installe nous avons montré que la connexion AI-ACC diminuait et probablement que l'énergie de cette connexion affaiblie ne permettrait plus de maintenir le déséquilibre entre DMN et CEN. Là encore cette hypothèse d'interaction entre les différents réseaux devra être démontrée.

Enfin, puisqu'un des objectifs de ce travail de thèse concernait la recherche de marqueurs de l'effort mental ou de la fatigue, nous avons mené une dernière étude au cours de laquelle des échantillons de salive ont été prélevés afin de comparer la concentration de cortisol avant et après l'accomplissement d'une tâche cognitive (imagerie motrice) et une tâche physique (tâche d'alerte).
Les données normatives concernant le taux de cortisol dans la salive se situaient dans les fourchettes suivantes: (i) collection du matin: 3,7 à 9,5 nanogrammes par millilitre de salive;
ii) collecte à midi: 1,2 à 3,0 nanogrammes par millilitre; et (iii) Collecte en soirée: 0,6-1,9 nanogramme par millilitre. Les analyses des taux de cortisol dans les échantillons de salive, n'ont montré aucune différence significative entre l'échantillon 1 (S1) et l'échantillon 2 (S2) dans la comparaison entre les groupes de l'étude.
En revanche, des analyses statistiques ont révélé une corrélation significative entre S1 et S2 ($p = .002$) en intra-groupe, notamment dans le groupe mental « grM ».

En imagerie, à partir d'hypothèses et d'analyses de régions d'intérêt (ROI) (hypothalamus et tronc cérébral), nous avons comparé l'activité cérébrale entre les groupes et dans chaque groupe (grM et grP), entre le début et la fin du run. La comparaison entre les deux groupes a révélé une activité accrue au niveau des régions d'intérêt notamment dans le grM comparé au grP. Des analyses individuelles ont montré pour les participants ayant une faible concentration de cortisol (P2 chez le grM et P4 chez le grP) que l'activité du tronc cérébral et de l'hypothalamus était plus faible et moins étendue chez P2 comparé au P4. Cependant, lors

de la comparaison statistique des participants ayant un niveau élevé de cortisol (P9 chez le grM et P10 chez le grP), une activité plus étendue était observée au niveau du tronc cérébral

Cette étude montre que la tâche d'imagerie mentale (comparée à la tâche motrice réelle) serait plus exigeante en termes de sécrétion de cortisol comme le démontre l'augmentation de l'activité cérébrale dans l'hypothalamus et le tronc cérébral (TC) connu pour réguler l'arousal. Le TC envoie des projections noradrénergiques ascendantes au travers du thalamus et vers les structures corticales (Cortex cingulaire antérieur, Cortex préfrontal et pariétal) pour maintenir l'arousal (Jones, 2003). Ce contrôle « bottom-up » proviendrait principalement de la partie ponto-mésencéphalique du tronc cérébral (Clemens et al., 2011, 2013).

De plus, au niveau du locus caeruleus, ces mêmes neurones noradrénergiques interviendraient pour réguler le stress (Papadimitriou & Priftis, 2009). Ces neurones projettent directement sur la partie de parvocellulaire de l'hypothalamus, plus précisément sur les noyaux hypothalamiques paraventriculaires (PVN) qui constituent le point de départ du circuit régulateur de la sécrétion de cortisol. Donc, au cours d'une tâche cognitive intensive, l'activité du tronc cérébral augmenterait pour fournir un niveau optimal d'arousal nécessaire pour accomplir la tâche.

Quand l'effort se prolonge dans le temps, l'activité du tronc cérébral diminue entrainant par conséquent une diminution des stimulations noradrénergiques envoyées vers les structures corticale (diminution de l'arousal) et vers l'hypothalamus (baisse de la concentration de cortisol). En outre, Kahneman (1973) appuie l'hypothèse que l'arousal et cortisol varieraient dans le même sens. Il considère que l'effort mental dans ses manifestations physiologiques, serait un cas particulier de l'arousal. Le cortisol pourrait donc constituer un marquer de l'effort mental puisqu'il est directement lié à l'activité de l'arousal. Ainsi, le tronc cérébral et l'hypothalamus pourraient constituer deux régions clé qui interviennent dans la régulation de la sécrétion de cortisol en réponse à une situation cognitivement exigeante.

En conclusion, les travaux de cette thèse s'articulent autour de deux grandes parties. La première partie pose le cadre théorique de l'étude et consiste à investiguer les bases temporelles de l'attention, son déploiement et les limites qui en découlent. La deuxième partie est centrée sur l'identification de déterminants psychologiques, et de marqueurs neuronaux et physiologiques de l'effort mental en vue d'une caractérisation plus intégrative de la fatigue mentale. Les résultats de ces travaux de thèse ont montré que le paradigme d'alerte muni de ses deux composantes (intrinsèque et extrinsèque) ainsi que la manipulation du paramètre comportemental foreperiod (FP) permettaient de mieux appréhender les processus

temporel de l'attention et leurs effets sur l'effort mental, notamment après une session courte et intensive d'une tâche d'imagerie motrice. Enfin, la mise en œuvre du protocole et la manipulation des blocs d'alerte au cours du temps , ont permis de développer et de proposer un modèle de circuits neuronaux (AI-ACC , AIDLPFC, ACC-DLPFC) permettant d'identifier les effets de l'effort mental au cours du temps.

En termes de perspectives, il serait intéressant d'intégrer l'ensemble des régions examinées dans un modèle de connectivité effective et fonctionnelle plus étendu dans lequel le tronc cérébral pourrait être considéré comme une structure centrale (hub).

Il serait également judicieux de coupler l'activité du cerveau avec des mesures physiologiques (fréquence cardiaque, respiration, dilatation de la pupille, réponse électrodermale) et d'ajuster les durées des FPs sur une échelle de temps au plus près des mesures physiologiques permettant de mieux caractériser les effets de l'arousal sur l'effort mental et la fatigue.

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Please find here the expression of my sincere gratitude and my deep devotion

I dedicate this work to my dear parents, my sisters, my brothers my friends and o all those who helped me achieving this work

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fMRI Randomized Study of Mental and Motor Task Performance and Cortisol Levels to Potentiate Cortisol as a New Diagnostic Biomarker

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List of abbreviations

RT	**Reaction time**
FP	**Foreperiod**
WS	**warning stimulus**
RS	**Response stimulus**
SRT	**Simple reaction**
SOA	**Stimulus onset asynchrony**
ISI	**Inter-stimuli-interval**
ITI	**Inter-trial-interval**
wMT	**With mental training**
MI	**Motor imagery**
woMT	**Without mental training**
WM	**Working memory**
DLPFC	**Dorsolateral prefrontal cortex**
ACC	**Anterior cingulate cortex**
AI	**Anterior insula cortex**
IPC	**Inferior parietal**
IFG	**Inferior frontal gyrus**
VENs	**Von Economo Neurons**
STS	**Superior temporal sulcus**
PFC	**Prefrontal cortex**
HC	**Hipocampus**
AG	**Amygdala**
HPA	**Hypothalamo-pituitry-adrenal**
PVN	**paraventricular nucleus**

ACTH	**Adrenocorticotropic hormone**
CRH	**Corticotropin releasing hormone**
CNS	**Central nervous system**
DMN	**Default mode network**
CEN	**Central executive network**
SN	**salient network**
PPI	**Psychophysiological interaction**
fMRI	**Functionalmagnetic resinance imaging**

General introduction

Theories in cognitive neurosciences describe the executive functions as a complex topic with many different aspects, they are assumed to be multifaceted systems (Humphreys, Donnelly, & Riddoch, 1993; Petersen & Posner, 2012; M. Posner, 1990; M. I. and S. J. B. Posner, 1971). Attention, one of the components, is considered as the most studied cognitive function of the human mind (Sarter et al., 2001)(Corbetta & Shulman, 2002; Demeter et al., 2011; W. Sturm et al., 2006). It is a faculty that we commonly use and adapt in our daily lives and constantly changing environments. So the ability to maintain attention over time is crucial for any adaptive behavior. (M. I. and S. J. B. Posner, 1971) have defined alertness, selectivity and orienting as the basic components of attention. These components make part of three large subdomains of attentional aspects: "intensive", "selective" and "orienting". These subdomains were well and differently investigated in the literature. However some of other aspects of attention in relation with time still relatively unexplored and weakly investigated. In this work, we propose to examine and clarify these theoretical concepts by proposing an approach and an explanatory framework of behavioral mechanisms in fMRI.

In fact, attention is distributed in space as well as time (Jennifer T. Coull, 2004). It has two big dimensions; "spatial dimension" and "temporal dimension". In our daily life our attention is quickly directed to the location and at that moment in which we expect the occurrence of a salient event. Both temporal and spatial eventualities optimize our behavior. Taking a simple example of the green and the red light in the street, it seems that our reactions are faster if our temporal attentional focus is directed to that moment in time at which we expect the light to turn from red to green. If the light changes sooner or later than expected, our reactions would be adjusted or delayed.

The perception of time is omnipresent in attention (Jennifer T. Coull, 2004), because the estimation of time flow is naturally sub-conscious and integrated when focused in a daily task. Albert Einstein defined time as duration "proper" to each object according to its location in space, but "time" is neither common, nor shareable between objects and individuals. From a neuroscientific point of view, time perception and time flow can be approached by manipulating the concentration and the components of attention sensitive to the passage of time, such as alertness.

Several experiments, using visual reaction time tasks with temporal cues, have been conducted to study temporal and cognitive processing of attention. They postulate that

subjects are significantly faster when they are asked to detect a target preceded by an informative cue compared to an uncued targets (Michael I. Posner et al., 1980) (Niemi & Näätänen, 1981). When a warning stimulus is presented for milliseconds before the imperative stimulus, the subject prepares to respond more efficiently to the target. However during the simple detection tasks participants has no information about target occurrence and attention is directed sub-consciously to target. Here we talk about what two distinct theories of visual attention "the goal-directed attention" and the "stimulus-driven attention" (Egeth & Yantis, 1997). The difference between these two conceptualizations is that one involves voluntarily guided expectancies based on cue validity and temporal instructions (Goal-directed attention) (Barnes & Jones, 2000; Michael I. Posner et al., 1980), and the other one involves fast involuntary attention driven temporally towards a unique single cue (Stimulus-driven attending).

Taking together, attention and time are therefore intrinsically linked. They undergo fluctuating and dynamic processes. "Time" is considered as information (factor) (Michon 1972) and it is a basic characteristic of presented stimulus. The duration of a stimulus and its time occurrence are determinants of performance. When engaged in a cognitive task, subject has to generate suitable strategies in order to produce consistent decisions, (when and how to respond). So, temporal factor influences the efficiency of cognitive information processing.

Understanding the mechanisms underlying the temporal processing fluctuations during an attention task, its deployment and its limits as a function of time can helps to better understand the temporal aspect of attention in general, and could help to deeply examine attention disorders in many clinical populations such multiple sclerosis and fatigue syndrome. So, the aim of this thesis work is to attempt to describe the psychological and neurophysiological mechanisms that underlie the temporal aspects of attention, allowing the rapid processing of information.

Here, alertness was chosen as the best suitable component to study temporal aspects of attention because it includes two fundamental concepts: "Arousal" and "Temporal expectancy" activated in motor preparation and execution tasks. In addition to that, variations in attention over time are often discussed in the literature in relation to concepts such as Sustained attention, Arousal, Vigilance and Alertness (Oken, Salinsky, and Elsas 2006). In other terms, changes in arousal or alertness are likely to produce fluctuations in temporal processing of information. Alertness is divided into intrinsic and extrinsic components and often assessed with reaction time tasks that require quick responses to presented stimuli. High

speed is taken to reflect a high level of arousal (Mottaghy et al., 2006; Michael I Posner & Rafal, 1987; W. Sturm et al., 1999, 2006). The parameters of a typically simple RT paradigm can differ from task to another: the warning signal (WS), the imperative stimulus or called also response stimulus (RS), the response itself or the reaction time (RT) and the foreperiod (FP) (Niemi & Näätänen, 1981).

Temporal preparation in time is a complex cognitive ability that optimizes behavioral responses when a target appears after a certain time interval, called FP (foreperiod). The ability to respond rapidly and predict the exact stimulus appearing moment during this interval, reflects a high level of arousal and high temporal processing which in turn involves anticipating and reasoning strategies. The FP includes two factors; (the FP length) and how it is distributed over all task trials (FP variability). These factors can directly affect the temporal processing and consequently the performance. Several recent studies have shown that during a simple RT task with variable FPs design, RTs are shorter for longer FPs, called "The foreperiod effect" (Capizzi et al., 2015; Jennifer T. Coull, 2009; Niemi & Näätänen, 1981). In addition, other studies have shown an interaction between two successive FPs called "sequential effect" (Drazin, 1961; Los & Van Den Heuvel, 2001; Steinborn et al., 2008; Vallesi & Shallice, 2007; Woodrow, 1914). In these studies, RTs were found to be slower when the previous FP was longer than the current one.

There are many debates in the literature concerning the different processes influencing the temporal preparation and the effects of FP duration. There has been a functional dissociation of the implicit temporal preparation related more to controlled and preparatory mechanisms consuming resources, and sequential effects that would support more automatic mechanisms. In this context, this thesis work focuses on studying the cognitive-temporal interactions in simple reaction time performance by exploring alertness as a basic component of attention and by using the FP as a principle behavioral component that would allow examinating the temporal attentional processing. We try to find psychological, neurological and physiological markers of mental effort for a better characterization and definition of the mental fatigue described in the life of every day, in education, sport, and neurological diseases as the chronic fatigue or multiple sclerosis. The originality of this work lies in the fact that we have used a multimodal approach combining psychological, behavioral, and functional analyzes. This methodological approach enabled us to study temporal fluctuations over very small time lapses (< 1s) and localize in fMRI neural structure responsible for that.

The implementation of a protocol combining simultaneously a cognitive-motor and an imaging task enabled us to bring out the cerebral regions involved in the temporal processing and constitute a first neural model of temporal deployment of attention within healthy population. This putative neural model is composed of three regions of the right hemisphere: the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate (ACC) and the anterior insula (AI). The DLPFC and the ACC were well investigated and known to be involved in cognitive tasks and especially in the control and maintain of alertness state. However, recent studies started to focus on AI as a basic component of alertness especially intrinsic alertness and have demonstrated that AI intervenes in the control of endogenous attention and helps to generate control signals necessary for the maintaining arousal and stable mode strategies. In addition, these three regions share a neuronal architecture called Von economo neurons which are characterized by speed conduction due to their large axonal size. The role of these neurons remains unclear, and they have been given an important role in the social domain, particularly in the speed of social decision-making and intuition (Allman et al., 2005).

In the first chapter of this thesis) we start by presenting a theoretical framework including the different conceptualizations that have served building the working hypothesis. In the second chapter (Study A), we focused on studying the temporal deployment of attention. We used visuo-motor imagery task as a mental training to examine how performance fluctuates behaviorally following various time frames changes (FPs). We purpose to show that attentional reinforcement induced by an intensive and short session of mental training, induces a temporal deployment of attention and allow optimizing the time pressure by maintaining a high state of arousal and ameliorating temporal preparation. In the third chapter (Study B), we try to show that when mental effort is maintained for a long time, sustained attention decreases and may lead to mental fatigue. This study deals with the question of whether cognitive processes of timing and expectancy during an alertness task also modify with increased effort trying to demonstrate that the putative neural model that we built would be a marker of mental effort or fatigue. Thus, we examined the following hypothesizes:

1- Numerous studies have shown that arousal, related more to the autonomic nervous system, is controlled by noradrenergic and cholinergic afferents originating from the brainstem (Jones 2003), Clemens et al., 2011; Gaspar, Berger, Febvret, Vigny, & Henry, 1989). These same studies have shown that arousal is a basic function of the right cerebral hemisphere (Langner & Eickhoff, 2013 (Sturm et al., 1999)) and have identified a fronto-parietal network that would intervene in the control of the arousal.

The right hemisphere is known to be involved in the activation of sympathetic pathways that would change automatically with homeostatic changes and implicated to respond to unexpected stimuli and urgent behaviors (Craig, 2005, Rogers & Andrew, 2002, Wittling, 1995; Jones, 2003; Robinson and Coyle, 1980). Based on the literature we hypothesize that visuo-motor imagery task used as mental training would improve the temporal expectancy and RTs would be shorter especially for short FP intervals which would be more sensitive to rapid arousal changes. We purpose to examine in fMRI effective connectivity of AI-ACC and AI-DLPFC circuits in the intrinsic alertness task and DLPFC-ACC circuit in the extrinsic alertness using different FPs ranging from 250ms to 710ms

2- We expect that, after 30 minutes (motor imagery + real physical task), the attentional resources of the participants would decrease, resulting in a behavioral increase of the RTs. The decrease in attentional resources could reflect increased mental effort and would be perceived as a mental fatigue and seen more during intrinsic alertness task. Decreased arousal woud be reflected in the temporal processing and would be associated with a decrease in effective connectivity of endogenous AI-ACC and AI-DLPFC circuits in particular at the shortest FPs

In the fourth chapter (Study C) we manipulated a physiological component “cortisol” to examine the relation between mental effort and cortisol activity which would constitute a physiological marker of mental fatigue. In fact, cortisol represents the stress hormone in humans (Herman, Ostrander, Mueller, & Figueiredo, 2005) released as response to a stressful situation. Many clinical studies have related low cortisol levels to several pathologies in which fatigue is a common symptom such chronic fatigue syndrome (CFS), multiple sclerosis (MS and and fibromyalgia (Fries et al., 2005; Nater et al., 2008). In addition to clinical population, many cognitively demanding tasks have been shown to elicit decreased cortisol level in some healthy individuals (Dedovic et al., 2009).

3- Finally, we hypothesize that the motor imagery task, perceived as more stressful and cognitively demanding task, would require higher cortisol levels than the real motor task and therefore would promote wider spread brain region activity especially in the brainstem, and hypothalamus which would be responsible for controlling cortisol activity.

Chapter 1: Theoretical background

Summary

In order to highlight the different mechanisms involved in the activity of the brain during alertness tasks, we have begun to review the main concepts and methodological conclusions in the fields of neuroscience. Thus, in the first part of this chapter we will describe the anatomical structures and functional organizations of alertness network and the different conceptualization of intrinsic /extrinsic alertness. We explain the concept of timing and temporal expectancy in attentional tasks and more precisely the foreperiod (FP) as a basic behavioral component of alertness tasks. Then, we present the cerebral regions involved in the cognitive control of alertness particularly the DLPFC, the ACC and the AI as well as the Von economo neuros as being a common neural basis between these structures. Afterward, we review in a second part the concept of mental effort / mental fatigue during alertness tasks and the neural changes related to this later. We present finally the relation between cortisol activity and mental fatigue and key regions involved in the control of this. At the end of this chapter we highlight the concept of the motor imagery as being a key component of this thesis experiments.

Part 1

I) Alertness

Alertness makes part of the intensive aspects of attention. According to (Berlyne, 1950), the intensity of attention is related more to the level of arousal which in turn depends on the modalities (visual, auditory) and the properties (complexity) of the stimuli to which the organism is exposed. (Kahneman 1973) considers that the intensive aspects of attention are related more to "effort" and that they are assumed to be divided into voluntary and involuntary selection. In fact there are two ways of allocating attention. Subjects can voluntarily allocate attention to the spatial location that may contain information which is important to immediate task goals (goal-directed attention). On the other hand, stimulus events can involuntarily capture attention (stimulus-driven attention). In addition, the effect of voluntary attention increases as a function of the duration between the target stimulus and the preceded cue (stimulus onset asynchrony or SOA). Involuntary attention is largest at short SOAs and decreases with increased SOAs (M. I. Posner, Cohen, & Rafal, 1982; Warner, Juola, & Koshino, 1990). Thus, the voluntary attention reflects extrinsic or phasic alertness however involuntary attention reflects intrinsic alertness.
Alertness is generally assessed with simple reaction time tasks (SRT). More precisely, intrinsic alertness is assessed by SRT tasks including basic target detection without distracting stimuli however extrinsic alertness is assessed by those tasks including alerting (warning) stimuli external to the subject environment. SRT tasks are chosen because they contain little computational processing demands, minimizing variance due to irrelevant factors like strategy or practice (Blatter & Cajochen, 2007; Lim & Dinges, 2008).

Alerting is controlled by a cortical distribution of the noradrenergic and the cholinergic systems. Communication between the brainstem and the cortical is mediated by the thalamus. Thus, the primary function of the thalamus is to relay sub-cortical *bottom-up activity* towards cortical structures necessary for intrinsic alertness and simultaneously to relay *top-down* signals from cortical areas back to brainstem structures during high cognitive tasks. This interaction between bottom up and top down activity provides a flexible dynamic control to regulate arousal and cognitive processing during alertness tasks.

The cognitive processes during alertness tasks is not entirely lateralized but controlled by both hemispheres, with lateralization changing with increasing task difficulty (Allen, 1983; Hoptman & Davidson, 1994). The right hemisphere plays a crucial role in maintaining the

attentional focus with endogenous manner; however the left hemisphere is recruited when selection demands increase.

1) Functional neuroanatomy underlying intrinsic alertness

Intrinsic alertness or "tonic alertness" or "arousal" or "vigilant/sustained attention", all are terms used interchangeably and refer all to the degree of awakness necessary to accomplish daily life tasks and which change over time depending on physiological factors like the circadian rhythm or the sleep–wakefulness cycle. Although impairments in the ability to select relevant from irrelevant stimuli are assumed to impact daily life skills and cognitive abilities (Sarter et al., 2001). Intrinsic alertness is generally experienced when subjects have to react repetitively to a single target appearing suddenly without any distracting stimuli. It reflects a kind of mental effort that changes with task difficulties. Thus, a rise in the demands increases the level of effort, arousal and attention in general (Kahneman 1973).

Many studies have investigated the neural base of alertness and have found that arousal/ intrinsic alertness (Langner & Eickhoff, 2013) is a fundamental function of the right hemisphere (RH). This right lateralization may be related, as suggested by (Helton & Warm, 2008), to attentional simplicity of typical vigilance attention tasks or simple detection tasks in which stimuli are presented continuously and there is no need to high cognitive processing.

In fact (Howes & Boller, 1975; Ladavas, 1987; Michael I Posner & Rafal, 1987) have reported a significant increase in simple visual and auditory RT within RH injured stroke patients who nevertheless still benefit from a warning stimulus (Lewin et al., 1996). This observation gives the evidence that RH lesions impairs strongly in the intrinsic alertness and not the phasic alertness.

PET and FMRI Studies on intrinsic alertness have shown the implication of a RH network for various stimulus modalities (auditory, visual and somatosensory stimuli) (JT et al., 1998; Kinomura, Larsson, Gulyás, & Roland, 1996; Paus et al., 2008; W. Sturm et al., 1999; Walter Sturm & Willmes, 2001). They revealed a midbrain–thalamic-cingulate network responsible for intrinsic alertness in addition to anterior insula (Clemens et al., 2011, 2013; Coste & Kleinschmidt, 2016; Sadaghiani & D'Esposito, 2015) which plays a crucial role in detecting salient events and generating bottom up control.

Arousal regulation arises from noradrenergic system (NA) particularly from brainstem monoamine nuclei inputs, such as those from the mesocortical dopamine system originating in the ventral tegmental area, and norepinephrine inputs from the locus coeruleus (LC)

(Barger, 1992; Crino et al., 1993). The role of noradrenergic pathways in alertness lies in providing an optimal level of arousal (M. Posner, 1990). Lesion studies in rats (Robinson, 1979; Robinson & Coyle, 1980) have demonstrated bilateral depletion of NA system which was strongest with frontal lesions suggesting a dynamic alerting regulation in the NA system originating from the LC and projecting most strongly to frontal areas. (W. Sturm et al., 1999) suggest that the ponto-mesencephalic activation would represent the noradrenergic part of the intrinsic alerting network which opens the gates of several thalamic nuclei thus being able to relay signals to the dorsolateral prefrontal cortex and inferior parietal lobe (Kinomura et al., 1996)(Paus et al., 1997)

In fact, the LC sends dense projections to the ACC (Neiuwenhuys et al., 1988). The ACC, in turn, intrinsically controls the brainstem activation system via the reticular nucleus of the thalamus, from where the up-coming noradrenergic activation is spread to several cortical regions for specific information processing providing a bottom up activity (Fernandez-Duque & Posner, 1997; Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008; Haas, Zavala, & Landisman, 2011; Kinomura et al., 1996; Walter Sturm & Willmes, 2001). The anterior cingulate is the frontal structure which serves as the central regulating component within intrinsic alertness neural network. It is responsible for task-dependent modulation of arousal by modulating subcortical structures activation that provides noradrenergic bottom-up activity (Mottaghy et al., 2006; Yanaka, Saito, Uchiyama, & Sadato, 2010) (Paus et al., 1997) toward frontal and inferior parietal cortices. Inferior parietal activity during intrinsic alertness could be explained as an activation of attentional system responsible for spatial orienting of attention (W. Sturm et al., 1999; Walter Sturm et al., 2004)(Fernandez-Duque & Posner, 1997) and it is most likely related to the bottom-up processing of relevance and salience of stimuli in order to facilitate rapid target detection (Corbetta & Shulman, 2002).

2) Functional neuroanatomy underlying extrinsic alertness

Phasic alertness refers to short-term response readiness following a warning signal, with peak readiness only lasting for millisecond (Michael I. Posner, 1978). The warning stimulus could be in the same or a different sensory modality as the target stimulus. It is used to inform the subject about stimulus target appearing contrary to intrinsic alertness in which subjects have no information about stimulus accuracy.

In the brain a very similar right-hemisphere cortical and subcortical network is activated during extrinsic alertness with different sensory stimuli (auditory, visual...) These activations were localized mostly in the dorso- and ventrolateral frontal cortex, in the anterior cingulate gyrus, in the inferior temporal gyrus; the inferior parietal lobule (IPL) as well as in the thalamus. However, When discrimination difficulty increases, the right-hemisphere dominance vanishes and cerebral activation turns into a more symmetrical activity pattern showing increased activity in a bilateral fronto-parieto-occipital network as well as in left anterior insula and putamen (Demeter et al., 2011; Langner & Eickhoff, 2013; Nebel et al., 2005). This effect was observed when comparing phasic alerting with intrinsic alerting (Walter Sturm & Willmes, 2001). These bilateral activations under the phasic alerting could be interpreted as a consequence of the warning stimulus. In fact during phasic alertness tasks subjects have to inhibit somehow their responses to the warning stimulus in an active way and respond at the prominent moment to the target (W. Sturm et al., 1999). The additional left activation is considered to be an indication of selective attention. This finding goes with studies on left-hemisphere lesions in which patients present with choice reaction deficits (Dee & Van Allen, 1973) show slowed down responses after a warning in a phasic alertness task (Tartaglione, Bino, Manzino, Spadavecchia, & Favale, 1986)

As described before, subcortical structures send projections to frontal cortices. During phasic alertness frontal-parietal–sensory regions (DLPFC/IPL) exert “top down” control on subcortical structures. This top down control is considered as a set of mechanisms designed to enhance and maintain more complex attentional processing. It reflects high cognitive processes known to facilitate discrimination between salient and irrelevant stimuli or distractors (Sarter et al., 2001)

The warning stimulus appearing before the target stimulus requires somehow anticipatory strategies and spatial attention that lead necessarily to strong parietal activations. In addition information about the target stimuli has to be stored temporarily in working memory activating by the fact the dorsolateral prefrontal cortices. In this sense, the inferior and dorsolateral prefrontal areas sub-serve executive control and working memory processing during phasic alertness (Banich et al., 2000; Banich & Noll, 1993; Corbetta & Shulman, 2002; Jäncke, Specht, Shah, & Hugdahl, 2003)From the parietal cortices, top-down information passes to the frontal areas responsible for executive control.

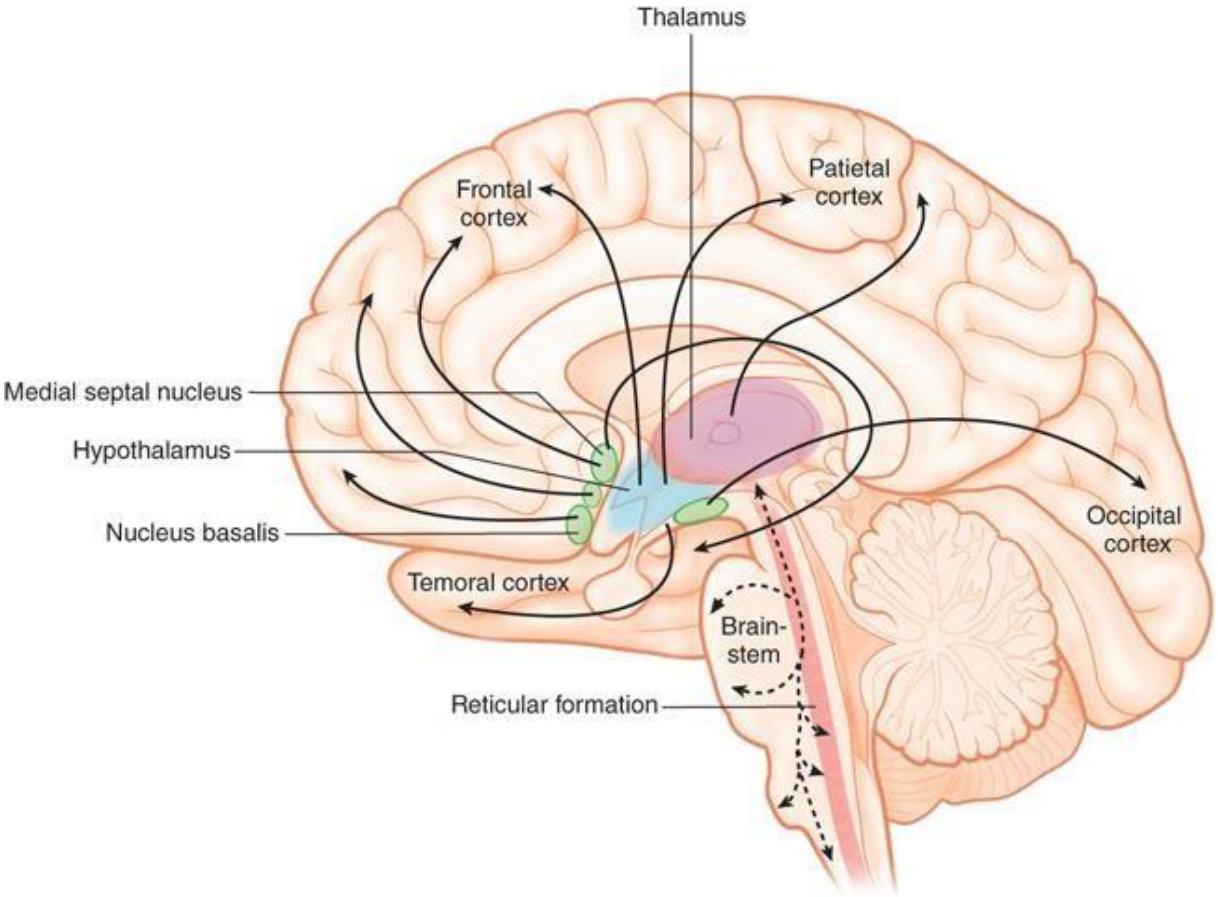

Figure 1. *Bottom up and top down dynamics during alertness tasks between subcortical and cortical structures*

II) Brain regions involved in the control of alertness

1) Thalamus and brainstem

Thalamus and brainstem share specific anatomical and physiological specializations that support their key role in the general functions of sustained attention, working memory, and motor preparation. Thalamus receives rich innervation from basal forebrain arousal systems as well as noradrenergic and cholinergic afferents from the locus ceruleus of the brainstem (Kolmac & Mitrofanis, 1999; Krout, Belzer, & Loewy, 2002). These innervations are known to activate neurons within the anterior intralaminar and adjacent paralaminar region (Schiff, 2008) which are interposed between brainstem/basal forebrain "arousal systems" responsible for thalamic, cortical activity and supervisory frontal systems activity (Parvizi & Damasio, 2001) that organize both adjustments of vigilance level or alertness (Michael I. Posner, 1978) and premotor shifts of attention (Rizzolatti, Riggio, Dascola, & Umiltá, 1987; Schlag-Rey & Schlag, 1984).

Ascending inputs to these neurons and their location make them particularly well positioned to play a role in arousal regulation (Schiff, 2008).

The central thalamic neurons play a crucial role in arousal regulation (Michael I. Posner, 1978). It has been demonstrated an important depolarization of central thalamic cells producing increased firing in the 20–80 Hz frequency band during wakeful state. Variations of temporal shaping and intensity of this activity occur in association with specific task demands. This activation is adjusted and controlled, across cerebral structures, basically by top-down signals from frontal regions involved in regulating effort and vigilance demands and bottom-up firing rates coming from brainstem arousal system (Schiff, 2008). According to human imaging studies, central thalamus occurs to be active during tasks requiring short-term shifts of attention and during tasks with high sustained demands of vigilance over extended period of time (Glenn & Steriade, 1982).

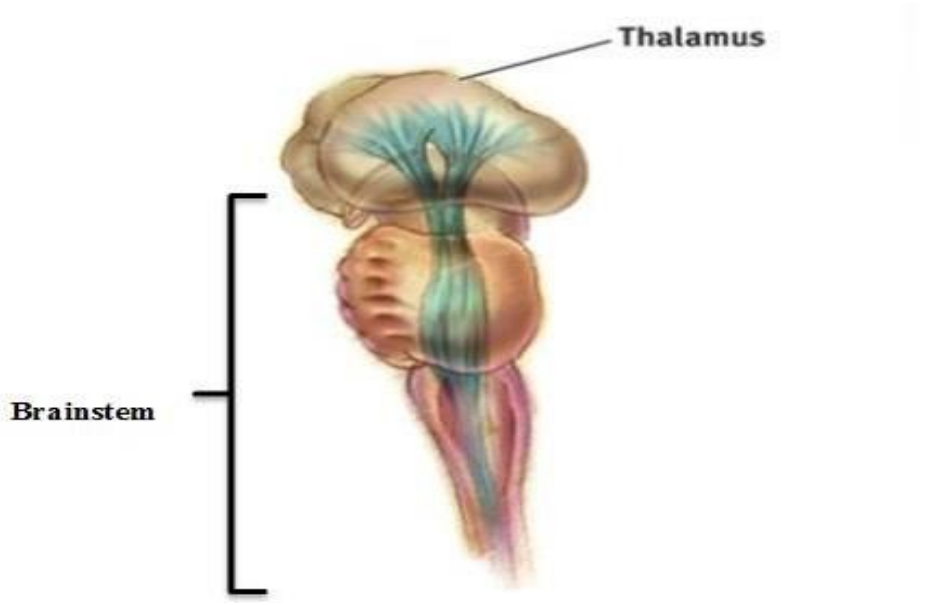

Figure 2: Brainstem and thalamus regions

2) The inferior parietal cortex

The inferior parietal cortex (IPC) is a posterior region of the brain that is most well-known for its role in visuospatial processing (V. E. Sturm, Haase, & Levenson, 2016). Regardless the spatial component, the IPC has a crucial role in maintaining vigilance and sustaining attention

(Adler et al., 2001; Foucher, Otzenberger, & Gounot, 2004; Häger et al., 1998; Johannsen et al., 1997; JT et al., 1998; José V. Pardo, Fox, & Raichle, 1991; Paus et al., 1997; Singh-Curry & Husain, 2009; W. Sturm et al., 1999; Walter Sturm et al., 2004). In fact, damage in the right inferior parietal cortex induces attentional deficits, indicating the implication of this region in the construction of attention gradients (Karhson, Mock, & Golob, 2015). Also, it has been demonstrated through Lesion studies, that lesion within the right hemisphere, for example in patients with tumor excisions (Rueckert & Grafman, 1996; Wilkins, Shallice, & McCarthy, 1987), causes impairments in the ability to sustain attention and respond to salient stimuli (Husain & Rorden, 2003)

Lesion data from hemineglect patients demonstrate that the right parietal cortex orients attention to both the left and right sides (Eriksen & St. James, 1986; Heilman & Valenstein, 1972). This result is supported by a study using independent component analysis in healthy adults (Karhson et al., 2015). (Corbetta & Shulman, 2002) have also identified a ventral attention network in the right hemisphere, including the inferior parietal cortex and particularly engaged when orienting to distractors that relate to the subject's task.

3) The dorsolateral prefrontal cortex: DLPFC

The dorsolateral prefrontal region roughly surrounds the principal sulcus, inferior convexity, and arcuate sulcus in the macaque monkey (Barbas & Pandya, 1991; Goldman-Rakic, 2011), it represents a combination of Brodmann's areas and Walker's areas 46, 9, and 10, in humans and macaques, respectively (Barbas & Pandya, 1991; Goldman-Rakic, 1987). The DLPFC is massively interconnected with other cortical and subcortical brain areas, as the prefrontal cortex as a whole (Barbas & Mesulam, 1981; Pandya & Yeterian, 1991).

The DLPFC has different functions such as detecting salient events, changing the focus of attention, engaging attention to new targets, preparing responses, dividing attention and maintaining a state of alertness (Corbetta & Shulman, 2002; M. M. Mesulam, 1999; Périn et al., 2010). Studies within humans and monkeys show that lesions in DLPFC cause marked impairments in working memoy (WM) tasks and in many aspects of focusing, dividing and shifting attention. So, DLPFC plays a crucial role in controlling WM capacity and several aspects of executive attention. Also, lesions in posterior and subcortical brain areas anatomically linked to DLPFC were found to impair WM capacity and attention control abilities (Kane & Engle, 2002). Thus, the DLPFC is central in the executive-attention processes of the WM system. It helps maintaining information in a highly active accessible state.

Furthermore the dorsolateral prefrontal areas particularly those anterior to the arcuate sulcus and surrounding the principal sulcus are critical to performance in the delay tasks (Goldman-Rakic, 1987; Rosenkilde, 1979). In fact, significant delay-task impairments were observed in macaques with temporary dorsolateral prefrontal damage (Bauer & Fuster, 1976; Quintana, Quintana, Fuster, & Fuster, 1993; Shindy, Posley, & Fuster, 1994; Stamm, 1961; STAMM & ROSEN, 1973). However, lesions in many other brain areas in ventral or superior PFC, often do not cause such deficits (Goldman, Rosvold, Vest, & Galkin, 1971; Mishkin & Pribram, 1955; Oscar-Berman, 1975; Zola-Morgan & Squire, 1985).

The DLPFC is known to play a fundamental role in the organization and preparation of forthcoming actions based on information stored in the working memory (Pochon, 2001). It is responsible for maintaining a high-level of preparation during waiting intervals. In fact, it has been demonstrated from single-unit recordings from DLPFC, significant neural cells population which begin firing when a target occurs and continue firing during the whole delay period until a response is produced. Such cells seem to keep the target-related information active or "on line"" during the delay period (J. M. Fuster, 1973; Joaquin M. Fuster & Alexander, 1973; Kojima & Goldman-Rakic, 1982, 1984; Kubota, Tonoike, & Mikami, 1980; Quintana & Fuster, 1999; Romo, Brody, Hernández, & Lemus, 1999).

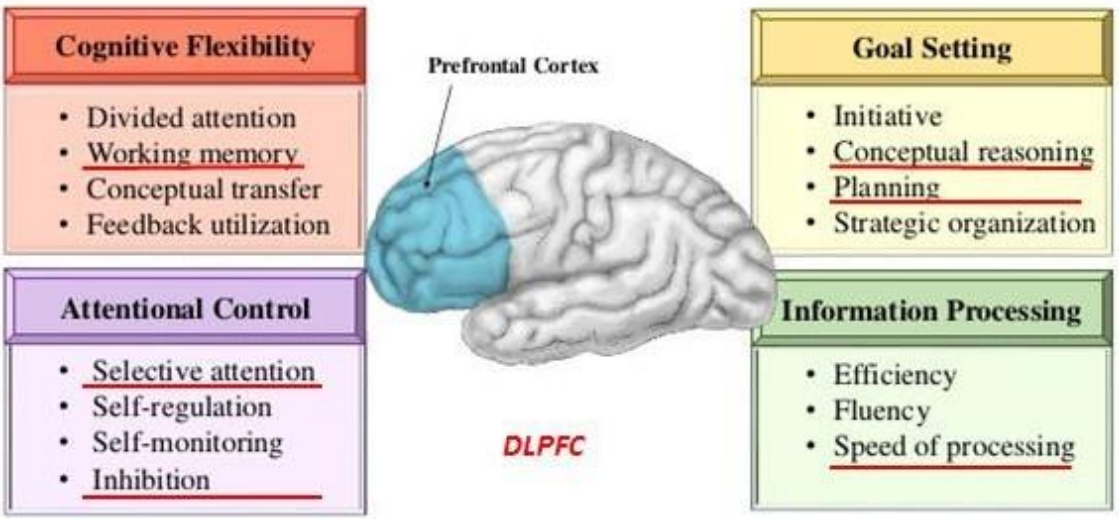

Figure 3: Functions related to prefrontal cortex (red underlined functions are associated particularly to the dorsolateral prefrontal cortex) (Anderson and Reid 2012)

4) Anterior cingulate

Many neuro-imaging studies have demonstrated that the anterior cingulate cortex (ACC) is involved in the executive control of cognition and behavioral regulation (Carter, Botvinick, & Cohen, 1999; Michael I Posner & DiGirolamo, 1998). It is implicated in several functions including pain perception, autonomic regulation, and higher cognitive function. Anatomically, the ACC has rich bidirectional projections to parietal, temporal and dorsolateral frontal cortices as well as multiple levels of the motor system, including SMA, pre-motor and motor cortex (He, Dum, & Strick, 1995). It also receives rich connections from the amygdala.

The ACC is assumed in general, to mediate attentional and executive functions and conflict monitoring in particular such as, error detection, performance monitoring and resolution of response conflict. It is well positioned to monitor information flow in the brain (M. M. Mesulam, Nobre, Kim, Parrish, & Gitelman, 2001; Miller & Cohen, 2001; J. V. Pardo, Pardo, Janer, & Raichle, 1990). Neuroimaging and PET studies (Paus, Koski, Caramanos, & Westbury, 1998) have demonstrated that the ACC makes part of the arousal system. It is richly interconnected to the noradrenergic (Gaspar, Berger, Febvret, Vigny, & Henry, 1989; M. -Marsel Mesulam, Hersh, Mash, & Geula, 1992) and cholinergic (M. -Marsel Mesulam et al., 1992) subcortical systems (Sarter et al., 2001), so it has an important role in the arousal modulation according to the task demands (Mottaghy et al., 2006; W. Sturm et al., 1999). It helps activating and facilitating responses (‘‘energization”) and sustain activation to respond (Alexander, Stuss, Shallice, Picton, & Gillingham, 2005; Stuss et al., 2005). The ACC activation is notably attributed to response selection when response selection is carried at a conscious/explicit level. (Corbetta et al 1999) have noticed increased ACC activity in divided attention task when subjects are required to select one or many stimuli across multiple features of a stimulus.

In addition to all these various functions, and as reviewed before, ACC has reciprocal connections to multiple levels of the motor system, so its activation has directly been related to the control of action particularly motor preparation. (Zysset et al., 2006) suggests that ACC is implicated in motor preparation before the participant producing a motor response. Also, disruptions of ACC neural activity has been found to cause deficits in the temporal control of action (Broersen & Uylings, 1999; Narayanan & Laubach, 2006). Taking together, the extensive connectivity between the ACC and cortical structures in one hand and motor cortices on the other provides powerful communication between motor and cognitive processing.

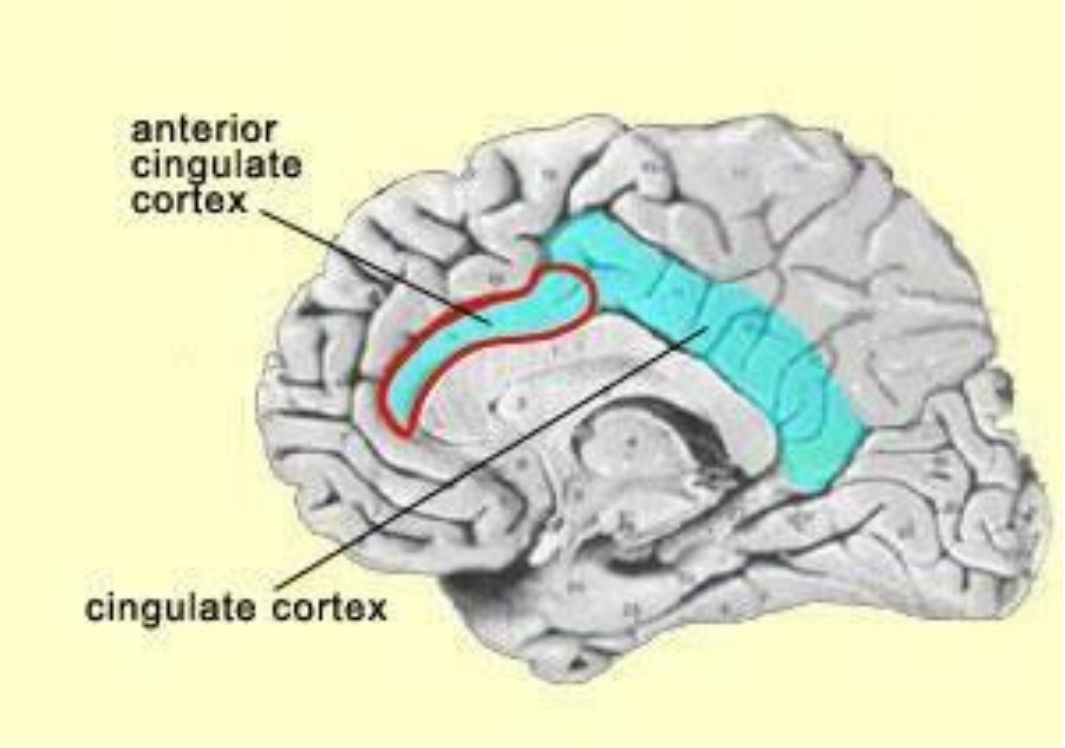

Figure 4: Cingulate cortex region

5) Anterior insula

Functional neuroimaging studies have shown that the right AI has multiple functions, it has been involved in the subjective awareness of both positive and negative feelings, such anger, disgust, judgments of trustworthiness, and sexual arousal (Craig, 2002). It has also been shown to be implicated in social cognitive processes such as deception.

the insular cortex is located within the lateral sulcus of the brain and has been considered to be paralimbic (M. -Marsel Mesulam & Mufson, 1982) or "limbic integration cortex" because it is densely interconnected to several limbic regions. It has efferent projections to ACC olfactory cortex, lateral orbital cortex, the amygdala, and superior temporal sulcus (STS), and receives input from olfactory cortex, orbito-frontal, ACC, and STS (Mufson & Mesulam, 1982)(M. -Marsel Mesulam & Mufson, 1982). (Craig, 2002) and colleagues have identified direct ascending pathways "homeostatic afferent pathway" from the spinal cord to both insula and ACC. The anterior insula receives also a direct projection from the basal part of the medial ventral nucleus of the thalamus, as well as important afferents from the central nucleus of the amygdala. Moreover, the anterior insula, itself, projects towards the amygdala.

This anatomical location of the insular cortex allows it to control autonomic functions by regulating sympathetic and parasympathetic nervous systems (Critchley, 2005; Oppenheimer, Gelb, Girvin, & Hachinski, 1992). It also has a role in the regulation of the immune system and participates in the interoceptive consciousness of the body (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). Furthermore, it has been involved in assessing the intensity of pain perceived by the body (Baliki, Geha, & Apkarian, 2009).

In addition, richly interconnected to the ACC, the AI intervenes in the detection of salient stimuli, whereas the ACC plays an important role in modulating (control and preparation) motor responses. Once a stimulus occurs, the AI initiates transient control signals involved in stable maintenance of task mode and facilitates task-related information processing in brain areas responsible for attentional, working memory, and higher order cognitive processes such as the ventrolateral / dorsolateral prefrontal cortex. Together, AI and ACC help to integrate bottom–up attention switching with top– down control (Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008)

Overall, AI is particularly involved in salient stimuli detection, bottom-up capture of focal attention, the initiation of task control and the maintenance of alertness (Han et al., 2018; Menon & Uddin, 2010; Sadaghiani & D'Esposito, 2015). It is considered as a functional key hub region in the human brain which initiates in a purely endogenous manner, a set of cognitive processes necessary for adaptive behaviors. Since endogenous control is the a fundamental process in human cognition, upon a salient sensory event occurrence, AI detects this event, generate transient signals and initiates a series of further processes to alert attentional information processing system to timely handle the event and rapidly oriented behavior toward the sensory event. This assumption goes with several studies, which associate the AI with maintaining vigilance, the transient capture of focal attention and many socio-emotional processing (Singer & Lamm, 2009).

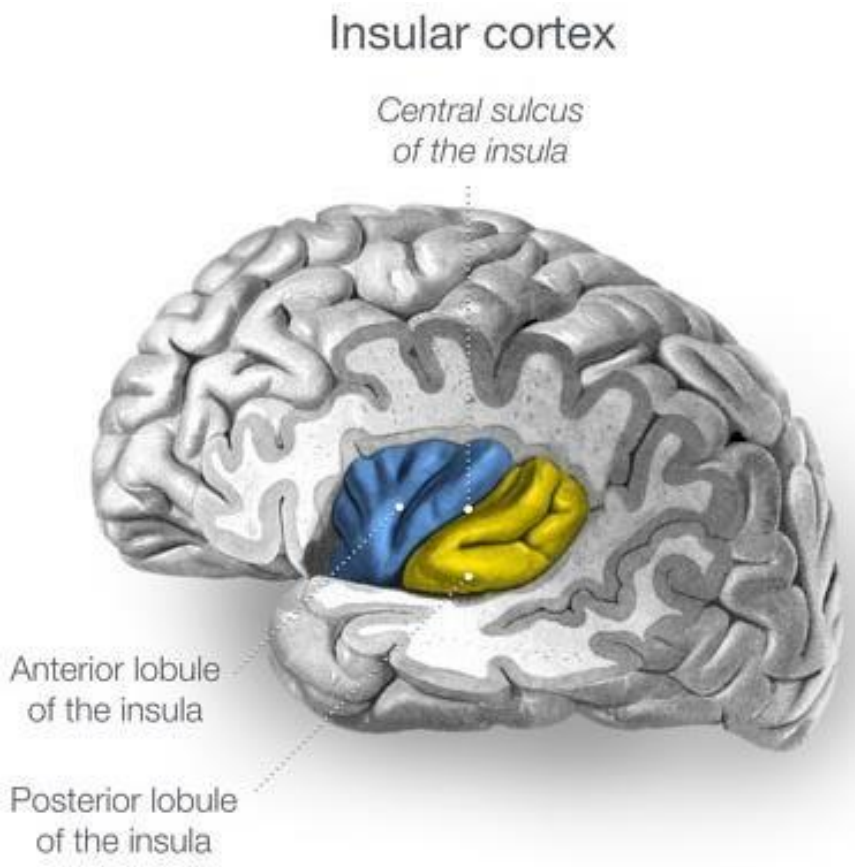

Figure 5: Insular cortex

6) Von Economo neurons (VENS): Common neural basis of DLPFC/ACC/AI network

The Von Economo neurons (VENs) are large, bipolar cells located in layer 5 of anterior cingulate (ACC) and frontoinsular (FI) cortex. The difference between these neurons and pyramidal neurons lies in the dendritic architecture; The VENs have a single large basal dendrite however pyramidal cells have a set of smaller basal dendrites extending from the cell (Allman et al., 2005). these neurons are a special characteristic of animals with big brains, they are observed in cetacean species such bowhead whale, killer whale, rossi's dolphin (Butti, Sherwood, Hakeem, Allman, & Hof, 2009; Hof & Van Der Gucht, 2007) as well as within common zebra, elephants and black rhinoceros (Butti & Hof, 2010; Butti, Raghanti, Sherwood, & Hof, 2011), (Hakeem et al., 2009). They occur notably within macaque monkeys whose anatomy is homologue to those found in humans. Big brains are naturally slower because of the long distances over which information flows. Also, large brains are

characterized by greater packing large myelinated axons which may represent a limit in information processing. But when we look deeper to large brain architecture, we notice that fiber pathways have small sets of very large axons. This may serve as a compromise to compensate for the packing constraint and facilitate rapid communication (S. S. H. Wang et al., 2008). Thus, the evolution of the VENs may be an adaptation related to large brain size.

It has been demonstrated through ontogeny as well as phylogeny studies that the VENs begin to develop in very small numbers in the 35th week of gestation and reach only about 15% at birth (postnatal stage). They attain an adult number by 4 years of age. The postnatal increase in VENs population may arise from migration from a potentially proliferative zone in the ventricles or some pre-existing cell type (Weickert et al., 2000). These neuros are known to be projection neurons; they send their axons through the white matter of the cingulum to other areas of other brain structures since ACC and FI cortex connect to prefrontal, orbitofrontal, insular and anterior temporal cortices, the amygdala, hypothalamus, various thalamic nuclei, and the periaqueductal gray (Cavada, 2000).

The VENs are densely located in the right hemisphere in infra-granular layers of the insula and anterior cingulate cortex of humans and chimpanzees. They are significantly numerous in the right comparing to the left hemisphere. In postnatal human brains and great ape, they are about 30% more numerous in the fronto-insular cortex in the right hemisphere than in the left (Benowitz et al., 1983; Weickert et al., 2000). These data indicate a strong and consistent predominance of the right hemisphere. This VENs asymmetry and rightward predominance may be related to the great cortical gray matter in the right fronto-insular cortex shown by fMRI studies comparing the left and right hemispheres within large healthy population (Watkins, 2001). It may also be associated with the asymmetry in the autonomic nervous system in which the right hemisphere is preferentially involved in sympathetic activation. In fact, the right hemisphere is related to sympathetic arousal and it is involved more to respond to the unexpected stimuli and urgent behaviors (Craig, 2005; Rogers & Andrew, 2002; Wittling, 1995). However the left hemisphere is related more to parasympathetic activity associated with high cognitive routines characterized with reduced tension and calming responses (Craig, 2005). Also may be because the right hemispheric is specialized in the social emotions (Benowitz et al., 1983; Blonder, Burns, Bowers, Moore, & Heilman, 1993).

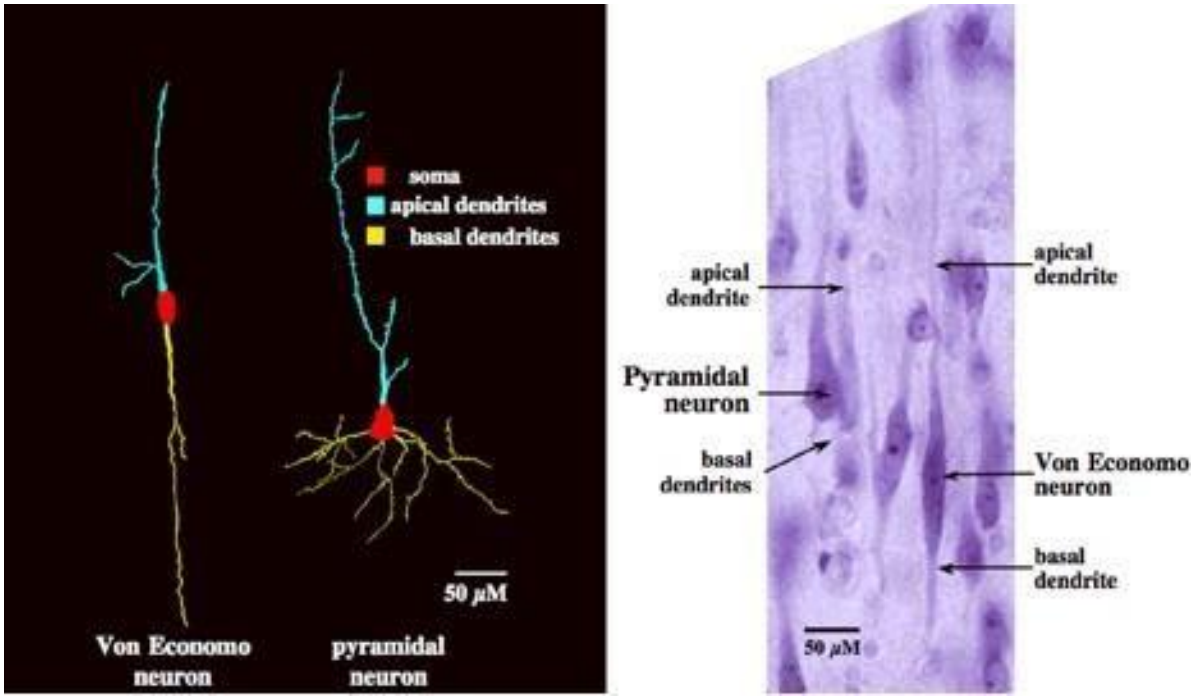

Figure 6: Large, spindle-shaped Von Economo neurons have a simple arrangement of two dendrites extanding from the top and bottom of the cell body (soma) - unlike the more complex pyramidal neurons of the cortex (John Allman 2005)

The functional role of these neurons is still elusive, it has been speculated that they are basically related to social cognition; social awareness and introception (Allman et al., 2005; Craig, 2009). In fact, both large brain size and complex social behavior allow rapid communication with other brain structures. Complex social behavior is often fast-paced, and this puts a premium on the capacity to respond quickly to changing conditions. Many studies have shown strange distribution and affected VENs in various populations who suffer from neuropsychiatric diseases that present impairments of social and communication skills, morality and self-awareness such fronto-temporal dementia, agenesis of the corpus callosum (Kaufman et al., 2008; Seeley et al., 2006), schizophrenia, (Brüne et al., 2010) and autism (Santos et al., 2011)

III) Temporal preparation / expectancy

Time occurrence of future event is a fundamental ability that we experience continuously during our daily life. Expecting the accurate timing of forthcoming events is important because it may facilitate information processing of high cognitive functions. An expected event gives rise to temporal awareness as planning, reasoning and anticipating strategies grow and attention becomes more focused in time (Scott w Brown 2008). Attention represents the process that helps to regulate what to use and what to filter out (Weinbach & Henik, 2012). The environment routinely provides spatial and temporal information, which can be used to generate contingencies about when and where a relevant event will occur. Thus, expectancy and temporal preparation help us to develop a state of preparation in advance of the occurrence of stimuli, so that attention can be focused on the specific locations and moments at which stimuli are expected to occur (Correa, Lupiáñez, & Tudela, 2005). Temporal preparation engages two distinct timing aspects: the explicit and the implicit timing. The difference between these two concepts is whether subjects have to provide an estimation of duration or not

1) Explicit timing

During explicit timing tasks, the estimation of a stimulus duration or the interval between two given stimuli is determined first, by *perceptual discrimination* ('perceptual timing'), in which subjects are able to visually distinguish between the temporal cue and the target and estimate the duration of each stimulus whether it is shorter or longer than another. Second *the motor timing,* in which subjects associate the timed duration or inter-stimuli-interval (ISI) with a sustained, delayed or periodic motor act. In all cases, the 'task goal' for the subject is to provide an accurate estimation of elapsed time (JT T. Coull & Nobre, 2008)

2) Implicit timing

During implicit timing tasks, on the contrary, instructions do not engage temporal estimation but require subjects to provide a perceptual judgement about stimulus characteristics or to perform a specific motor act. Despite the absence of temporal estimation of stimulus or motor act duration any temporal component underlying the rate of stimulus presentation or motor execution will implicitly engage timing mechanisms. Implicit timing could be determined either by *emergent timing* which is indexed by temporal regularity of a motor output timing resulting from the dynamics of motor control (Spencer, Verstynen, Brett, & Ivry, 2007;

Zelaznik, Spencer, & Ivry, 2002) or by the temporal predictability of perceptual input timing used to expect next stimulus occurrence (JT T. Coull & Nobre, 2008)

So there is an implicit use of timing to create temporal expectations. This mechanism may be subconscious 'exogenous' or conscious 'endogenous'. Exogenous temporal expectations are engaged fortuitously as the result of a temporally regular stimulus structure. However endogenous temporal expectations are engaged when subjects make explicit use of a warning pre-cue or regular waiting interval to predict stimulus occurrence. In both cases, temporal expectations are used to accelerate and improve accuracy task goals (Barnes & Jones, 2000)(Correa et al., 2005; Niemi & Näätänen, 1981; Praamstra, Kourtis, Hoi, & Oostenveld, 2006)

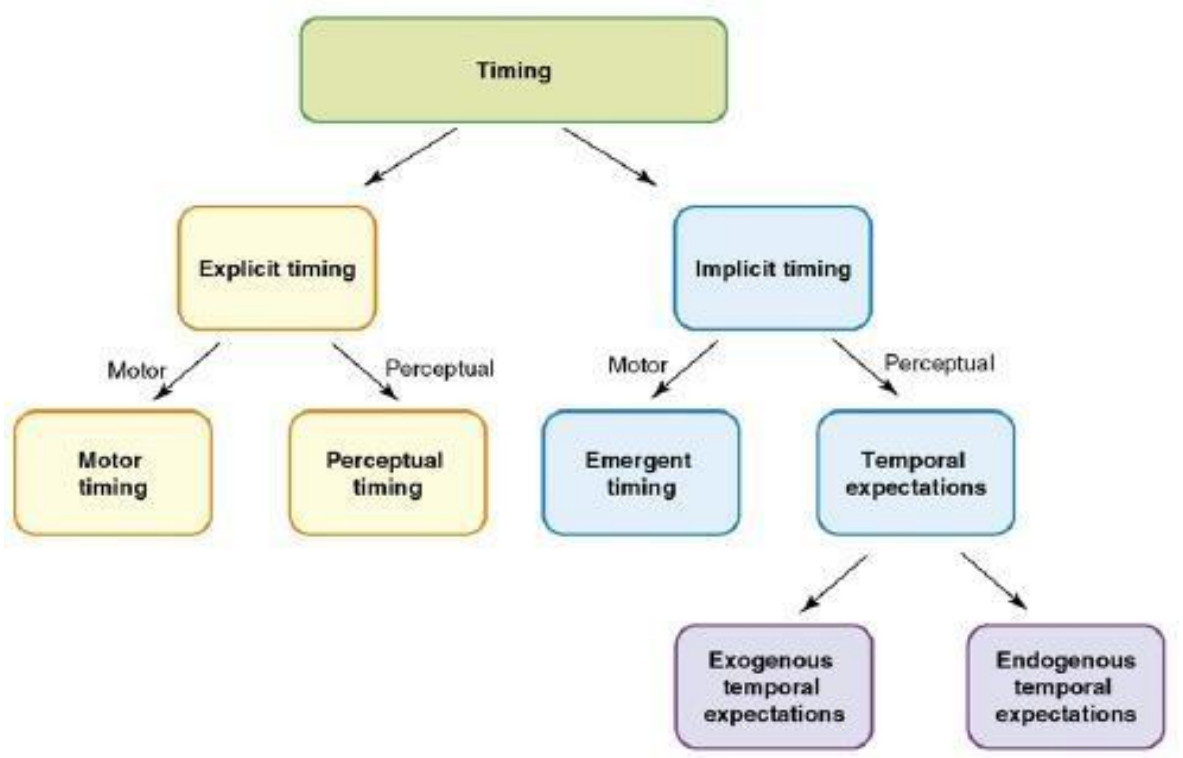

Figure 7. Explicit timing is engaged by tasks requiring either motor production (motor timing) or perceptual discrimination (perceptual timing) of a timed duration. Implicit timing is engaged as a by-product of the temporal regularity of either a motor output (emergent timing) or a perceptual input (temporal expectation) (Nobre and coull 2008).

During phasic/extrinsic alertness, temporal expectancy/preparation is triggered by an external stimulus or warning stimulus (endogenous conscious expectation). This latter reduces temporal uncertainty allowing better preparation and anticipation of target stimulus onset. When temporal certainty is relatively high, discrimination performance is better because the

response decision is then based on a greater amount of accumulated evidence .This indicates that temporal cues might be useful in distinguishing relevant from irrelevant information and might help with selecting targets within a temporal stream of distractors.

Temporal preparation helps participants to optimize their responses by reducing uncertainty about upcoming events and increasing probability of target stimulus occurrence to better respond at the prominent moment (Vallesi, Mussoni, et al., 2007). It is a cognitive concept that has been extensively investigated in studies using reaction time tasks and manipulating the so called foreperiod (FP) which is considered as a miniature vigilance situation where alertness must be developed rapidly and maintained over a relatively brief interval (M. I. and S. J. B. Posner, 1971)

Temporal preparation efficiency depends on the duration of the interval between the offset of the warning stimulus and the onset of imperative stimulus (FP). Researches on temporal preparation in which FP has been systematically varied indicates that RTs are shorter for longer FP "the FP effect". Warning cues usually produce faster motor execution of response to an imperative target compared with no-cue conditions (Weinbach & Henik, 2012). There is also what we call "the sequential FP effect" which represents the effect of the FP of the precedent trial on performance of the current one. Series of studies have shown that longer FPs on the preceding trial produce slower RTs on the current one (Niemi & Näätänen, 1981) (Vallesi, Shallice, & Walsh, 2007). More specifically, temporal preparation can reach an optimum at duration of 700ms. This duration is enough to increase arousal and allow subjects to adjust their attentional resources to produce better performance. Under 500ms the warning stimulus is no longer called "warning" but "accessory" stimulus (Welch & Warren, 1986, (Hackley et al., 2009)). Some studies have shown that even accessory stimuli can produce benefit on reaction times. Brief foreperiods give also rise to arousal shortening by the fact RT (Bernstein, Rose, & Ashe, 1970; Michael I. Posner, Klein, Summers, & Buggie, 1973). So both warning and accessory stimuli facilitate involuntary (reflexive) and voluntary reactions (Hackley et al., 2009; Hackley & Valle-Inclán, 2003). The underlying mechanisms of these two types of motor response may be assumed to overlap since for both types of stimulus, the RT varies as a function of foreperiod duration (Sollers & Hackley, 1997).

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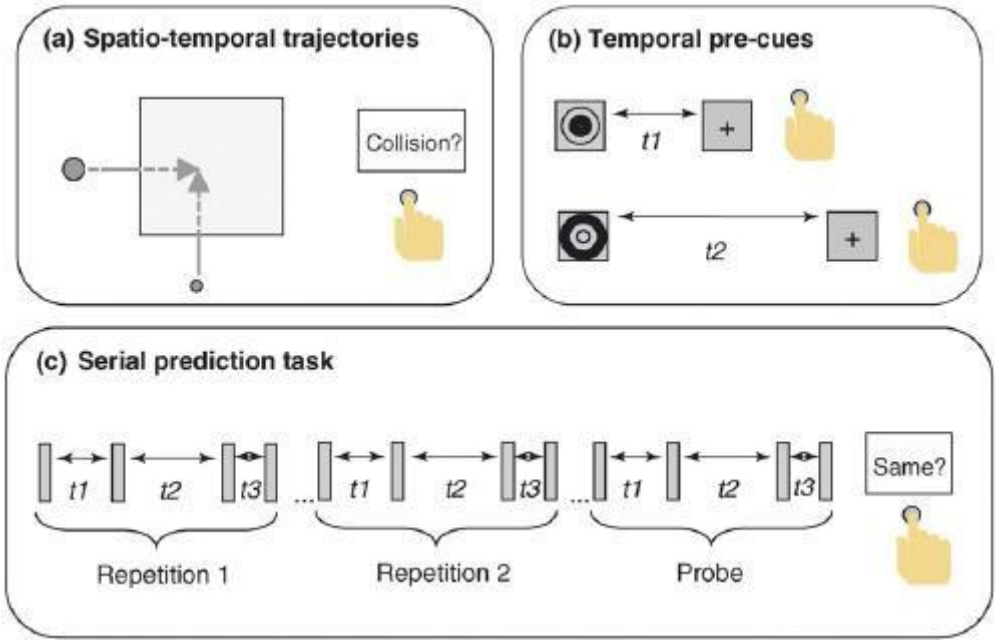


Figure 8: (a) Subjects implicitly use temporal information inherent in the speed of a moving sensory stimulus to predict its eventual location. Responses generally take the form of a perceptual discrimination. (b) Temporal pre-cues. Subjects learn temporal associations between symbolic cues and short (t1) or long (t2) inter-stimulus intervals (ISI). Subjects make deliberate use of this information in cued reaction-time tasks to predict when a target will appear and so speed its detection. (c) Serial prediction task. Subjects learn temporal patterns of target ISIs in order to estimate whether or not a probe sequence shows the same temporal pattern. Responses take the form of a perceptual discrimination. (Nobre et coull 2008)

3) Fore-period and relation to Reaction Time

The foreperiod is the behavioral component used to assess temporal preparation. It "provides the temporal frame of reference in which a subject prepares to respond to the imperative stimulus on a certain trial" (Niemi & Näätänen, 1981). It represents in general the time gap between either, informative or non-informative stimulus, and the imperative stimulus. During a simple reaction time, if subjects are able to estimate the FP length, they will be able to increase their readiness and adjust their willingness to react. Time uncertainty about the occurrence of the target stimulus is inversely related to the accuracy of the timing process (Klemmer, 1956, 1957). The more time uncertainty increases the more the level *of* expectancy decreases (R Näätänen & Merisalo, 1977). It is therefore important to know how long the FP is and how FPs of different length are distributed within a block of trials and during the whole task. The probability of estimating the exact moment of RS appearance

depends primarily on the FP length (R. Näätänen, Muranen, & Merisalo, 1974). It has been suggested that the speed of reaching the preparation peak depends on the nature of the WS; its modality and psychophysical intensity since stimulus modality is a determent factor of the reaction time speed. Studies addressing the modality problem have found that auditory WSs are more arousing than visual ones (Bertelson & Tisseyre, 1969; R. Davis & Green, 1969)

a) Classic FP effect

This model assumes that, during experimental designs, The foreperiod duration could either remain constant, making the timing of the imperative stimulus or response stimulus (RS) entirely predictable, or could vary randomly between different values according to a given probability design. If FP duration remain constant through a given task trials, the longer the FP is, the longer the RT (Klemmer, 1956; Woodrow, 1914). Here, it appears that with relatively short FPs, both accuracy of predicting the moment of stimulus presentation and reaction speed have been found to decrease as a function of FP (R. Näätänen et al., 1974) and time uncertainty increases significantly with longer FPs. However, If FPs are randomly presented within a block of trials and equally distributed through a given task ‘‘variable foreperiod design’’ RTs would be shorter for longer FPs, this is what we call ***“the classic foreperiod effect”*** (Capizzi et al., 2015; Jennifer T. Coull, 2009; Niemi & Näätänen, 1981). In fact, according to this distribution temporal readiness reaches an optimal level for longer FP than for short ones.

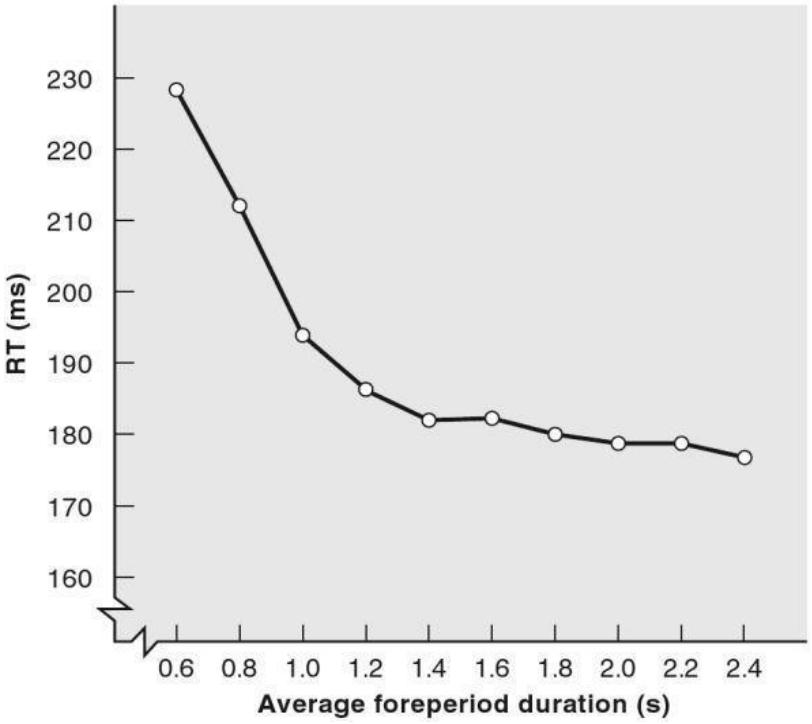
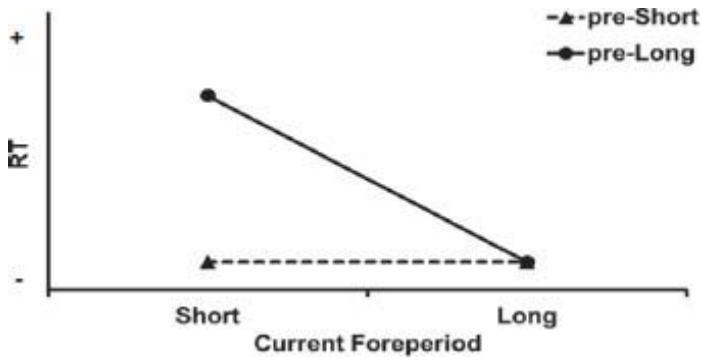


Figure 9: Effects of foreperiod, foreperiod variability, and probability of stimulus occurrence on simple reaction time (Drazin, D. H. (1961)

b) Sequential FP effect

It has been demonstrated that the duration of the preceding FP (short, long) and the whole trial has a strong influence on the current performance or RT. This phenomena is called "the sequential effect" which is manifested by a significant interaction between the current FP and the preceding one (Drazin, 1961; Los & Van Den Heuvel, 2001; Steinborn et al., 2008; Vallesi & Shallice, 2007). It reflects the ability of the participant to reorient his/her reaction to the critical moment that was the imperative moment of the last trial (Nobre & Coull, 2010). This strategy is optimal when the last FP is shorter than the current one since the interaction between both FPs is known to be asymmetric in general. In other terms RTs for current short FP are shorter for short–short FP sequences than for long–short sequences (Drazin, 1961; Los & Van Den Heuvel, 2001; Vallesi & Shallice, 2007). To be more explicit, RTs are longer when the current FP is shorter than the preceding one, compared to when it is equal or longer.



. ***Figure 10:*** *Asymmetric sequential foreperiod effect. (Mariagrazia Capizzi et al. 2015)*

c) Sequential effect models

There are two basic models that were developed to explain such effects; the trace-conditioning model proposed by (Los & Van Den Heuvel, 2001) and the dual process model proposed by Vallesi and colleagues (Vallesi & Shallice, 2007). These two models differ with regard to the mechanisms underlying them.

❖ *Trace-conditioning model*

According to (Los & Van Den Heuvel, 2001) "the trace conditioning is a form of classical or operant conditioning defined by a blank inter-stimulus interval between a conditioned stimulus and an unconditioned stimulus". These authors assume that the development of a conditioned response after a training acquisition is time locked to the conditioned stimulus and obtains its optimum at the unconditioned stimulus moment presentation (Gallistel & Gibbon, 2000; Grossberg & Merrill, 1992; Machado, 1997; S. Roberts, 1998)

This assumption relies on 4 putative rules (Los, 1996). First, the adjustment of state of conditioning corresponding to each critical moment is controlled by learning rules of trace conditioning. When a critical moment is bypassed in time, the state of conditioning engages a dynamic increase and a deterioration related to response activation. Second, the conditioned response takes much more time to accumulate and decay its asymptotic value decreases when the time interval between the critical moment and the warning signal is long. Third, if a critical moment coincides with the imperative moment on any trial, the conditioned response strength corresponding to this critical moment is reinforced. Fourth, and most important characteristic of the model, if the critical moment occurs before the imperative moment on any trial the conditioned response strength is extinguished, whereas it is still unchanged if the imperative moment precedes the critical moment (Los & Van Den Heuvel, 2001)

In its simplest form, according to the trace-conditioning model each critical moment is associated with conditioned strength. If the conditioned strength is high at a specific moment, RT would be shorter if the imperative stimulus occurs at this moment. This model is based on fundamental rules: Reinforcement, extinction and persistence. First, the current short FP benefits from reinforcement since it was presented and responded to in the previous trial, so the conditioned strength associated with any critical moment increases when the imperative stimulus is presented and responded to "reinforcement". Second, low preparation (as revealed by longer RTs) in the long–short FP sequence would be due to "extinction" of the conditioned strength associated with the short FP since it was bypassed in the previous trial by a longer FP. Finally, conditioned strength associated with critical moment that occurs later than the imperative moment remains the same "persistence".

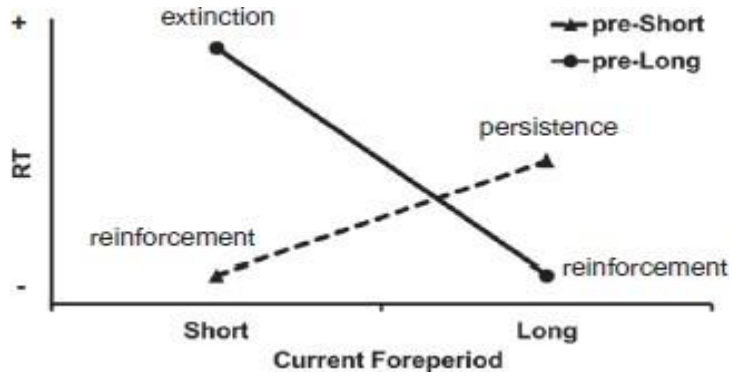


Figure 11: *Trace conditioning model of sequential effect (Mariagrazia Capizzi et al. 2015)*

- ***The dual-process model***

This model postulates that sequential effects are operated and sustained by non-strategic mechanisms generated during the previous trial such tonic arousal modulations deriving from the preparation duration of the previous trial (Vallesi & Shallice, 2007). It is assumed that a state of preparation at a critical moment is subject to two different influences; the conditional probability of imperative stimulus occurrence developed during the FP of the current trail n and the arousal modulation coming from last trial n-1. According to (Vallesi and colleagues 2007), RTs would be shorter when the previous foreperiod has been short rather than long because long–short foreperiod sequences are attributed to reduced arousal (or readiness to respond) since at the current foreperiod participants are still fatigued from having prepared for a longer period of time in the previous trial. So, the shorter FPn-1, the greater is the participant's level of arousal on trial regardless the duration of FPn.

It is conceivable that, on the dual-process account (Vallesi, Mussoni, et al., 2007; Vallesi, Shallice, et al., 2007), arousal deteriorates with increasing time interval between trials. Thus, increased inter-trial interval (ITI) brings arousal levels closer to baseline values and affects negatively performance (reaction time RT) of the current trial since RT facilitation to short-

short FP sequences is time-sensitive. So this facilitation effect decreases with long vs. short ITIs.

The dual-process model considers the variable FP effect as also a function of strategic monitoring process which estimates the conditional probability increasing of target occurrence during the FP duration and this to optimize behavior (Elithorn & Lawrence, 1955; Vallesi, McIntosh, & Stuss, 2009). The longer the FP, the highest probability is, thus explaining the RT benefit during this condition. Monitoring process is considered as an effortful and resource consuming process, so for a long inter-trial-interval (ITI) participants have much more possibilities to optimally prepare to respond to a target. Consequently, a greater FP effect (shorter RTs for longer FPs) is related more to a long ITI than to short one.

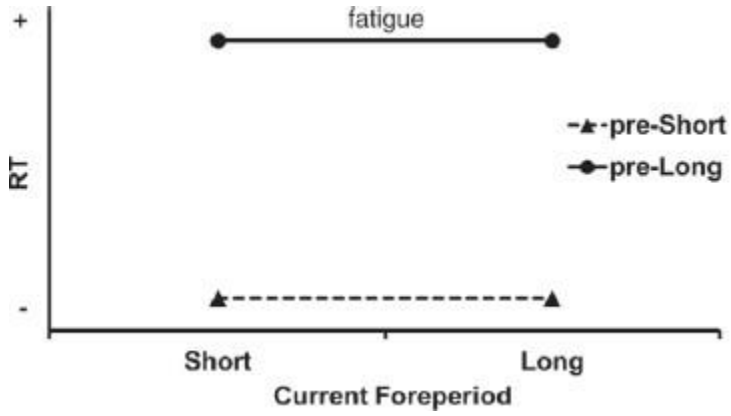


Figure 12: *Dual process model of sequential effect. (Mariagrazia Capizzi et al. 2015)*

IV) Neural basis of temporal preparation

Temporal preparation is basically a function of right prefrontal cortex. Lesions studies, (Stuss et al., 2005), show that the classical FP effect disappeared within patients with right lateral prefrontal lesions. These patients find difficulties to increase their readiness to respond as time goes on and fail to check whether a stimulus has occurred over laps of time. (Vallesi, Mussoni, et al., 2007) have notably shown a reduction in the FP effect after surgical removal of tumors of the right prefrontal cortex. Also (Teixeira Ferreira et al., 1998) have shown that patients with focal lesions of the prefrontal cortex could maintain visuospatial information in short term memory, but were mostly impaired when this stored information had to be linked to a forthcoming sequence of actions. These studies support the hypothesis that right lateral prefrontal cortex is the seat of the critical process producing the FP effect

Temporal preparation makes part of higher cognitive functions since it implicates various processes such as planning, anticipating and reasoning. These processes require the ability to maintain information in short-term memory and manipulate this information to organize an appropriate goal-directed behavior (Pochon, 2001). In fact DLPFC has been extensively implicated in in the cerebral network of working memory and this in studies of animals (monkeys) (J M Fuster, 1997; Petrides, 1994) and humans (Owen, 1997; Smith & Jonides, 1999).

Within Monkeys, electrophysiological studies have shown sustained neuronal activities in the DLPFC during the delay periods. This neural activity may be attributed to the short-term maintenance of internal representations of perceptual information and the set of preparation processes (Barone & Joseph, 1989; Funahashi, Bruce, & Goldman-Rakic, 1991; Quintana & Fuster, 1999; Sawaguchi & Yamane, 1999) suggesting that the DLPFC may play a critical role in linking between the information maintained in short term memory and the organization of the forthcoming actions (J M Fuster, 1997).

(Stuss et al., 2005) have reported that damage in frontal region (brodman area 46/9) may produce inefficient transfer of information and that these patients have difficulties in time perception. More explicitly they do not perceive time accurately about stimulus occurrence; as a consequence they hey could not perceive the ongoing time flow of the inter-stimulus-interval and increase their preparedness and predictability for the upcoming stimulus. Also a transcranial magnetic stimulation (TMS) study by (Vallesi, Mussoni, et al., 2007) confirmed the neuropsychological finding of (Stuss et al., 2005) on healthy participants in showing that the inhibition of the right DLPFC by the TMS induces a reduction in the FP effect.

In addition to time perception impairment induced by frontal lesions (Mangels, Ivry, & Shimizu, 1998), monitoring deficits (monitoring the occurrence of stimuli over time) have been also related to patient with superior medal frontal damage (brodman area 24 32). In fact the role of these regions is energizing (excitation of the relevant cell assemblies) and facilitating temporal processing. They are most often active in the presence of a non-specific warning stimulus (non-informative cue (Los & Van Den Heuvel, 2001). The non-specific warning stimulus reduces RT and this reduction in RT is originating from the facilitation process during the laps of time between the warning and imperative stimuli (Facilitation is generally considered to be optimal at intervals between 200 and 500 ms (Niemi & Näätänen, 1981).

Part 2

I) Mental effort

(Kahneman 1973) postulates that the completion of any mental activity requires an information input, and a nonspecific input, called "effort," "capacity," or "attention" which are according to him three interchangeable terms. So effort is considered as a case of attention and inversely attention is considered as a surge of mental effort. The amount of effort invested in a task depends on the intrinsic exigencies of the task and the personal /voluntary control that one can produce over time. Different mental activities impose different demands, a simple task demands little effort, and a difficult task demands much. Thus, as task demands increase, allocating less effort than the standard probably increases the gap and the discrepancy between task demands and personal resources causing a deterioration of performance. Allocating more than the standard, is considered to exceed our abilities. There must be a distinction between the *momentary* effort and the total amount of effort that necessary to accomplish a giving task. It is assumed that momentary attention or effort is controlled by a feedback from the execution of the whole current activity.

Mental effort has been related more to the intensive aspects of attention and more particularly to “arousal” or “vigilant attention” and it is largely controlled by the properties of the stimuli to which the organism is exposed (Kahneman 1973). The occurrence of novel stimuli induces a surge of arousal which represents, at least in part, a surge of mental effort (Kahneman 1973). Physiologically, mental effort is considered as a special case of arousal. The effort that a subject produces at a specific moment corresponds more to what he/she is actively doing, rather than to what is passively happening to him (Kahneman 1973). According to (Kahneman 1973) when a person is engaged in a cognitive task, arousal and effort vary physiologically second by second following the demands imposed by the task. When the effort provided does not meet the demand, performance decline entirely because allocating less effort than the standard causes a deterioration of performance.

(Pribram & McGuinness, 1975) postulated also that effort used during a attentional mental reflects the energy required to produce changes in the "representational organization of information processing". Task difficulty and complexity are known to increase subjective perception of mental effort which have been related to increased conductance responses, heart rate, and heart rate variance in studies measuring physiological arousal (Lundberg &

Frankenhaeuser, 1980; Smit, Eling, & Coenen, 2004a). Thus subjective perception of mental effort may reflect changes in arousal during performance of attentional tasks.

The conception of mental effort has been associated to *time-pressure* which is considered as an important determinant of effort (Kahneman 1973). All mental tasks involve probably time pressure. Tasks imposing strong cognitive load implicate severe time-pressure comparing to easy tasks. The concept of time pressure is characterized by the "speed" which reflects the rate at which someone executes a task or a sequence of tasks. It is sometimes imposed by explicit instructions to accelerate performance and sometimes by specific task characteristics. The decrease of speed causes a disproportionate increase in the sense of strain.

II) Cognitive fatigue as a consequence of prolonged mental effort

Mental activities experienced during our daily lives impose different cognitive demands depending on the nature of circumstances and situations. When an activity is prolonged in the time the cognitive demand increases rising by the fact the level of attention and consequently mental effort. When mental effort is sustained a long period of time "excess mental effort" it can lead to mental fatigue which is defined by (broadbent 1971) as a "time-related deterioration in the ability to perform certain mental tasks".

In general, sustaining attention during prolonged alertness tasks increases mental effort perception. Continuous performance requires a stabilization of attentional mechanisms in order to maintain task engagement (Banich et al., 2009, 2000). This process of stabilization is known to be effortful and cognitively demanding (Mulder, 1986; Michael I. Posner, Cohen, Choate, Hockey, & Maylor, 2019; Sarter, Gehring, & Kozak, 2006). The resistance to intensive long periods of mental effort can negatively affect a cognitive performance manifesting in, the failures in target detection (Loeb, Davies, & Parasuraman, 1984) and the increase of RT (Boksem, Meijman, & Lorist, 2005). The inability to sustain attention and the failure in maintaining an efficient cognitive performance results from a depletion in attentional resources (Grier et al., 2003; Wright, Stewart, & Barnett, 2008). The result of this resource depletion is a failure to control and maintain a stable allocation of cognitive resources to the task at hand (Lorist et al., 2000; Robert & Hockey, 1997). In this case we talk about "strain", exhaustion" or "mental fatigue". As a consequence, when fatigued, the implementation of task-mode and cognitive strategies is no longer maintained at optimal levels, and performance declines. Thus, a state of mental fatigue is characterized by the inability to allocate sufficient processing resources to a giving task (Matthews & Desmond, 2002; Smit, Eling, & Coenen, 2004b).

III) Brain regions involved in mental fatigue

In healthy populations, neural changes, related to prolonged cognitive tasks or "mental fatigue" have been studied and were associated with areas that are active during an optimal engagement of attention. Several studies have found decreases of cerebral blood flow (CBF) over the time within a large right network including posterior cingulate cortex, middle frontal gyrus (Lim et al., 2010), dorsolateral PFC, inferior parietal cortex and thalamus (JT et al., 1998), bilateral ventrolateral PFC, inferior frontal gyrus, temporal parietal junction and anterior insula (Breckel, Giessing, & Thiel, 2011). The decrease of CBF in these different areas was exclusively driven by vigilance tasks. However during a discrimination task which requires selecting between two or more responses (cues), Coull and colleagues (JT et al., 1998) found changes neither in RT nor in right inferior frontal or parietal cortices over time. Whereas, in a study by (Paus et al., 1997), during a 60 min auditory discrimination task, time-related CBF decreases were found in a right-lateralized cortical network including ventro- and dorsolateral PFC, parietal and temporal cortex, as well as in mainly left-sided subcortical structures (thalamus, putamen). All of these studies probably reflect deactivations that we could observe in fMRI. In addition to healthy populations, mental fatigue is known to be the most developed symptom within many clinical populations who suffer from neurodegenerative pathologies such as Alzheimer's disease, patients with Chronic Fatigue Syndrome (CFS) (Fukuda et al., 1994), and especially Multiple Sclerosis (MS) (Camp et al., 1999; DeLuca, Genova, Hillary, & Wylie, 2008). These populations have real difficulty to exert and sustain mental effort in tasks that require focused or divided attention.

IV) Mental fatigue and relation with cortisol activity

1) Cortisol

Cortisol is an adrenal corticosteroid secreted as a result of the hypothalamic-pituitary-adrenal (HPA) axis activation. It is the stress hormone in humans (Herman et al., 2005) released as response to a situation in which demands are perceived to exceed personal resources (Ledoux, Thompson, Iadecola, Tucker, & Reis, 1983). It targets both peripheral and central neural systems (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; McEwen, 1998). Cortisol level is known to be high upon awaking, (an increase of cortisol concentration about 50—60% as estimated following awakening "the cortisol awakening response or CAR"), and declines over the rest of the day, reaching a very low concentration around midnight. Thus, a

balanced regulation of cortisol activity is necessary for the maintenance of homeostasis human state (McEwen, 2000; Tsigos & Chrousos, 2002).

Animal studies have shown the involvement of some brain structures like brainstem nuclei and some specific limbic system structures such as the hippocampus (HC), the amygdala (AG), and the prefrontal cortex (PFC) in the control of cortisol secretion and this by exercising regulatory functions on HPA axis (Herman et al., 2003). Depending on stressor factors either "physical" or "psychological", it has been suggested that the brainstem in involved in physical stress, while psychological stressors tend to engage limbic system regions.

the paraventricular nucleus (PVN) of the hypothalamus represents the key target of these various structures (Herman et al., 2003). Cells within the PVN release corticotropin releasing hormone (CRH) upon stress perception, this hormone travels through the infundibulum to stimulate the pituitary gland, which in turn releases adrenocorticotropic hormone (ACTH) (Dedovic et al., 2009). This latter stimulates the adrenal gland to secret cortisol. Cortisol regulates its own secretion via a negative feedback circuit in the central nervous system (CNS), where it sticks to specific receptors throughout the limbic system (Feldman & Weidenfeld, 1995; Herman et al., 2005).

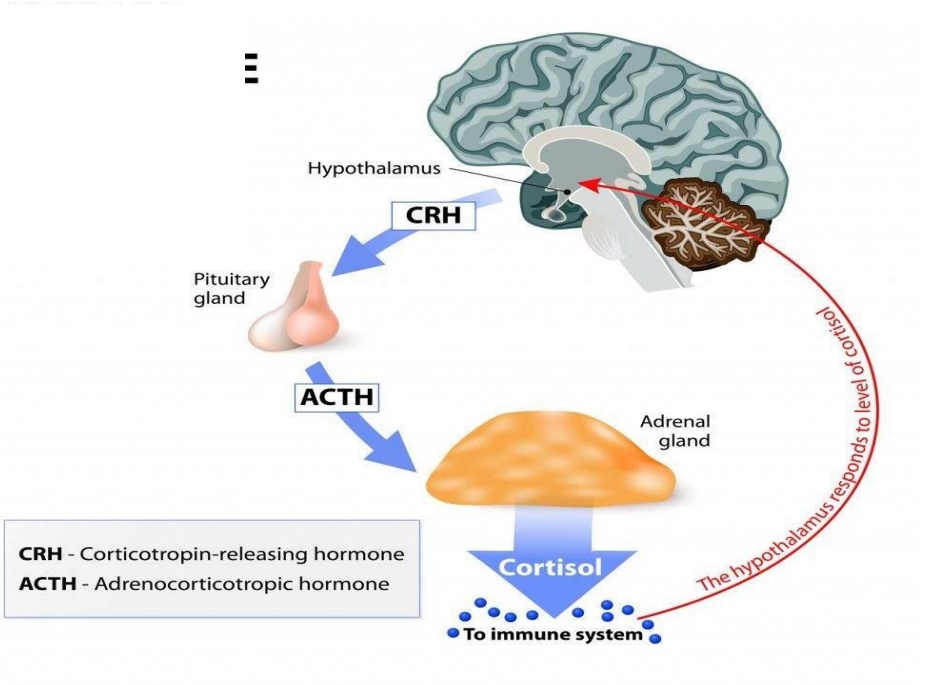


***Figure 13**: circuit of cortisol regulation (John A. Catanzaro 2019)*

2) The relation between Fatigue and cortisol secretion

The relation between fatigue and cortisol appears to be complex because it depends whether fatigue is accurate or chronic. It is unclear whether alterations in cortisol secretion play a role in the development of fatigue or whether changes in cortisol develop later as a consequence of fatigue and related syndromes (Candy et al., 2003; S. Wessely et al., 1995). Cognitive fatigue in general is a state of psychological stress, it can be defined as arising from the 'prolonged performance of cognitively demanding tasks requiring sustained mental efficiency' (Lorist, 2008) Cortisol secretion as a consequence of fatigue state depends also on various factors such as sex, circadian rhythm, the nature of the task on hand and on the population (some individuals show a significant cortisol response (called responders) and individuals who do not (non-responders)).

Many clinical studies on chronic fatigue syndrome (CFS) and fibromyalgia, in which fatigue is a common symptom suggest that these syndromes have low levels of the adrenal corticosteroid cortisol (Fries et al., 2005; Nater et al., 2008). In addition to clinical population, many cognitively demanding tasks have been shown to elicit a cortisol stress response in some healthy individuals. In fact, (Dedovic et al., 2009) have investigated the relationship between cortisol response and fatigue condition within healthy population and have revealed significant interaction in the right hippocampus over time. This interaction reflected significantly decreased cortisol level.

3) Regions implicated in cortisol regulation

a) Hippocampus

The hippocampus (HC) plays a central role in cortisol regulation given the high concentration of cortisol receptors in this area (Elissa B et al. 2013). It is known to exercise a tonic inhibition of the HPA axis and upon stress perception this inhibition is removed allowing the increase in cortisol secretion. During a tress task, an inverse correlation between cortisol response and hippocampal volume was observed (J. C. Pruessner et al., 2005). Furthermore, another study reported that HC volumes were inversely associated with cortisol levels after hydrocortisone administration (Tessner, Walker, Dhruv, Hochman, & Hamann, 2007)These studies confirm the role that would have the HC in cortisol regulation in showing larger cortisol responses associated with smaller hippocampal volumes.

b) The amygdala

The amygdala (AG), a critical part of the limbic system, is known to be implicated in threatening processing stimuli (Adolphs, 2008; Bishop, 2008)and play a major role in regulating the stress-related glucocorticoid secretion (Jankord & Herman, 2008). It stimulates the activation of the HPA axis when the organism is exposed to a stress (either physical or psychological). It has been reported that increased AG activity leads to an increase of adrenocorticotropic hormone (ACTH) in humans (Gallagher, Flanigin, King, & Littleton, 1987), and variations in cortisol levels has been shown to modify AG activation in response to stressful situations (van Stegeren et al., 2007). In addition, AG is involved also in adjusting the level of arousal depending on the salience of the stimuli and plays a crucial role in monitoring the environment in general (M. Davis & Whalen, 2001).

c) Prefrontal cortex

Prefrontal cortex and its specific components (orbitofrontal PFC, ventrolateral PFC and medial PFC) intervene actively in the processing of the cortisol regulation and stress response. It has been demonstrated during a psychological stress task a decreased orbitofrontal PFC activity associated with increased cortisol concentration (M. Pruessner, Pruessner, Hellhammer, Bruce Pike, & Lupien, 2007; J. Wang et al., 2005). Similarly, increased activity in medial PFC regions was related to decreased cortisol secretion (Kern et al., 2008). The ventrolateral PFC has direct connections to the HC; it has also some projections to the ventromedial PFC. Under stressful situation the ventrolateral PFC decreases activity in orbital and medial PFC to increase cortisol secretion.

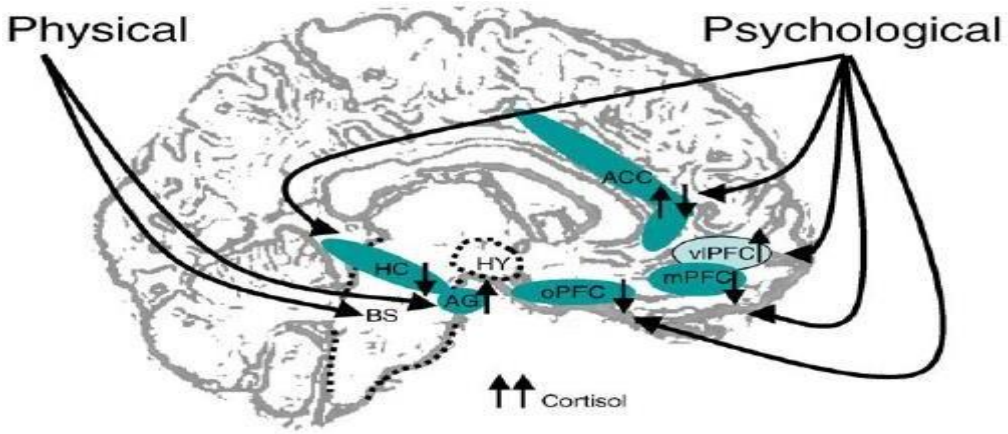


***Figure 14**: Basic framework of brain areas involved in processing physical and psychological stressors (Dedovic et al. 2009)*

Part 3

I) Motor imagery

Motor imagery has been defined as the conscious mental simulation or rehearsal of actions involving our brain's motor representations in a way that is similar to when we actually perform movements (Jeannerod, 1995). It corresponds to a dynamic process by which the brain activates a motor plan and monitors its unfolding through internal feedback signals, while maintaining moto-neuronal output in a state of tonic inhibition or subliminal activation.

The concepts of motor imagery is a cognitive operation which can be performed in different modalities and in numerous areas of research such sport psychology, cognitive psychology, and notably cognitive neuroscience. It may be experienced in two ways. The first person perspective, which is supposed to rely on motor-kinesthetic information processing (Kinesthetic MI) and the third person perspective, which would rely more on visuospatial processing (visual MI) (Decety, 1996). Kinesthetic MI requires individuals to "feel the movement", to perceive the sensations normally associated with its execution such as muscle stretching and contractions, whereas visual MI requires individuals to self-visualize the execution of the movement (Guillot et al., 2009)

II) Motor imagery modalities:

1) Kinesthesis motor imagery

Kinesthetic MI is especially used in the domain of sport and athletic training, in order to reinforce the importance of the kinesthetic component of a movement over its visual aspect. **"**It corresponds to an active process in which the human body is involved and during which the representation of a specific action is reproduced internally within working memory without any overt motor output" (Decety & Grèzes, 1999; Jackson, Lafleur, Malouin, Richards, & Doyon, 2001a). During this experience, subject feels himself performing a specific action or a sequence of actions. (Jackson, Lafleur, Malouin, Richards, & Doyon, 2001b) concluded, that the internal imagined images emphasize the kinesthetical feeling of movements and activate subconsciously the different mechanisms and processes involved during motor task .

2) Visual imagery

Visual imagery requires self-visualization of a movement from a first (internal visual imagery) or third-person (external visual imagery) perspective. The first-person perspective corresponds to the representation of a movement as if the individual takes part to the action himself, hence suggesting that he/she would visualize the movement like having a camera on his/her head. By contrast, the third-person perspective corresponds to the representation of the movement as if the subject was a spectator and that somebody (himself or another person) performed the action (Guillot et al., 2009)

III) Motor imagery: A mental training with significant cognitive content

When the act of imaging a movement is repeated a few times, we talk about "mental practice" or "mental training" which consists of a training method by which the internal reproduction of a given motor act is repeated extensively with the intention of learning a new ability or improving a known skill. Mental practice with MI requires that subjects have all the necessary declarative knowledge about the different components of the task before practicing. Thus, it is important to distinct between the act of imaging motor movement "motor imagery" which refers to a specific cognitive operation, and the act of repeating an imagined movement "mental practice" which designate a training method that can use various cognitive processes, including motor imagery. So using motor imagery repetitively represents a mental training that helps to optimize performance cognitively, by stimulating working memory and increasing vigilance, and physically, by improving motor execution.

Several studies have shown that mental practice helps optimizing the execution of learned movements and the acquisition of new skills as well. It is a method through which performance can be facilitated and improved. In fact, According to (Jeannerod, 1994, 1995)motor imagery (MI) represents the result of conscious access to the content of the intention of a movement, which is usually performed unconsciously during movement preparation. He concluded that conscious motor imagery and unconscious motor preparation share common mechanisms and are functionally equivalent. This may be the reason why mental practice using MI training results in motor performance improvements (Feltz & Landers, 2016).

In general movements either imagined or executed are subject to common laws and principles (Jackson et al., 2001b) they almost share a common neural substrate. When a subject is mentally imaging the execution of a movement, signals are sent to target muscles. The same

neu-romotor pathways that are involved in the execution of a specific action are activated also during mental practice. This activation helps improving the appropriate coordination patterns and strengthening motor pathway in the motor cortex (Mackay, 1981; Magill, 2007; Page, Levine, Sisto, & Johnston, 2001). Furthermore, it has been shown a significant congruence in temporal relationship between imagined and executed movements (Cerritelli, Maruff, Wilson, & Currie, 2000; Decety, 1996).

The timing of movements, either performed physically or imagined, engages same processes (Jackson et al., 2001b)Mental training by motor imagery allows subjects to rehearse the cognitive components of a task "symbolic learning theory" (Sackett, 1934). According to this theory, movements are symbolically coded in the working memory, making them easier to execute (Janssen JJ et al.1994). Several studies which have used mental training are consistent with this theory reporting that mental training includes a strong cognitive content (Feltz & Landers, 2016; Yue & Cole, 1992). Indeed, the "cognitive demands" necessary to imagine a given task depend on it complexity, simple tasks like pressing a bottom or drawing are less complex than performing motor acts like producing a sequence of movements or walking around obstacles.

It has been proposed that motor imagery might be considered as a neuronal process which involves specific brain structures. Apparently, these structures are of basic importance for the cognitive control and planning of movements. It has been shown that motor images share the same neural mechanisms as those that are also responsible for preparation and programming of actual movements (Decety, 1996; Luft, Skalej, Stefanou, Klose, & Voigt, 1998)

Part 4

I) Methodological techniques

1) fMRI principles

Functional Magnetic resonance imaging is a technique which has been shown an undeniable progress for over 20 years in the understanding of brain function and its plasticity in healthy humans as in the context of many pathologies. (Roy & Sherrington, 1890),were the first in to theorize that cerebral blood flow might reflect neuronal activity which was later confirmed by establishing that cerebral blood flow correlated with neuronal consumption in glucose (Raichle, 2011). At the microvascular level (capillaries and venous micronetworks), brain activity causes vasodilatation and thus a modification of the ratio between hemoglobin oxygen (oxyHb) and free hemoglobin (deoxyHb): the first will then tend to increase, the second to decline. However, the magnetic behavior of these two entities is different: oxyHb, like most tissues, is diamagnetic, that is to say, it tends to decrease the magnetic field to which it is exposed, while in contrast, deoxyHb is paramagnetic. It results in a local inhomogeneity of the authenticated magnetic field by an increase in the signal intensity collected on the T2 * weighted sequences when a brain zone is activated.

This dependence of the signal intensity on the content of oxy- and deoxyHb is called a BOLD effect (or contrast for Blood Oxygen Level Dependent). The first applications of the analysis of the BOLD effect in humans have made it possible to highlight active brain zones during the performance of a given task or the exposure to a stimulus within the framework of the fMRI protocols. Unfortunately, these data have sometimes reinforced the idea of functional localization before the newer conceptions of network organization take over.

Activation MRI also has certain limitations: it only targets subjects who are able to effectively perform the task requested, task paradigms are limited because of the installation in the MRI, the report signal / noise is important given the limited temporal resolution of the machine, the directions and temporality of links between brain areas are sometimes difficult to grasp and the analysis is often performed network by network while brain function is intrinsically interconnected.

2) Effective connectivity principles

The fMRI allows to approach, according to different treatment processes, the data of functional and / or effective brain connectivity. The common principle of these two approaches is to identify brain areas / networks activated either during the execution of a task or exposure to an experiment or even during resting state

Here, we will focus on effective connectivity method of analysis in fMRI, which are most often implemented during task execution but also sometimes during rest protocols (Roebroeck, Formisano, & Goebel, 2005). Some are guided by assumptions such as structural equation modeling (SEM) or dynamic causal modeling (DCM), they then require to identify networks of interest. Other methods are exploratory (data-driven), such as the model for studying psychophysiological interactions (PPI).

Effective connectivity refers explicitly to the influence that one neural system exerts over another, either at a synaptic or population level. (Aertsen & Preissl, 1991)proposed that ‘‘effective connectivity should be understood as the experiment and time-dependent, simplest possible circuit diagram that would replicate the observed timing relationships between the recorded neurons.’’ This speaks to two important points: effective connectivity is dynamic (activity-dependent), and depends on a model of interactions or coupling (Friston et al., 1997)

Chapter 2/ Study A: Temporal deployment of attention by mental training

Summary

In this study we focused on the characterization of the temporal deployment of attention using two alertness tasks (extrinsic and intrinsic) as basic components of attention which mobilize temporal processes of the motor response. We have manipulated arousal and optimized the temporal preparation using a motor imagery task (15 minutes) and different inter-stimuli interval durations called foreperiods (FPs)) which were equally distributed and randomly presented within eight blocks of trials ranging on a scale from 250 ms to 710 ms according to a variable FP design model. Before and after the entering to the scanner, participants underwent neuropsychological tests including the d2, the trial making test and the stroop test, in order to assess the temporal speed capacities and executive functions of the subjects. Behavioral results showed that the mental training task permitted to optimize temporal expectancies with a decreasing of the reaction time during both alertness tasks, notably to the shortest FPs (250/280ms for intrinsic alertness and 650ms for extrinsic alertness) ,as well as an increasing of the attentional functions. From an effective connectivity analysis in fMRI, we have proposed a putative neural model, primarily composed of three regions: the anterior insula (AI), the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC). In the intrinsic alertness task, imaging results showed a significantly strengthened effective connectivity from circuits emanating from the right anterior insula with ACC and the right anterior insula with DLPFC for the shortest FPs (250/280ms); in the extrinsic alertness task, we observed a significantly strengthened effective connectivity from the dorsolateral prefrontal cortex to ACC, also for the shortest FPs (650ms). These neural circuits corroborate the behavioural outcomes obtained previously. The neuropsychological performances were consistent with a functional connectivity increased in the regions of interest. This study demonstrate that by manipulating the FPs and mental training, we modulate arousal which increases with mental training and highlight a neural network that would be responsible for temporal deployment of attention.

I) Introduction

Many fMRI studies on attention have tried to understand "where" and "how" attention is controlled in the brain using different components of attention (Clemens et al., 2011, 2013; Mottaghy et al., 2006; Périn et al., 2010; W. Sturm et al., 1999), but no study has focused on the temporal deployment of attention after mental training. In fact, the temporal aspect of attention represents the ability to anticipate and prepare for actions and orient rapidly attention to a giving point in order to achieve daily life goals. This natural ability engages the use of strategies and eventualities in order to adjust attention according to situations and circumstances (Los et al. 2014). Understanding the behavioral mechanisms and potential circuits that participate in temporal processing constitute a real challenge that may contribute as an opening for clinical researches especially within population who suffer from attentional deficits such as the inability to switch rapidly attention from target to another, the failure to maintain arousal, to prepare for actions and sustain optimal temporal preparation as time goes.

As said in the general introduction, attention is characterized by a temporal and a spatial dimension, expecting when a target will appear is helpful to expect where to orient attention because efficiently directing attention towards a particular moment in time can be helpful to direct spatially attention to a particular location (Jennifer T. Coull, 2004). Temporal orienting includes motor and perceptual preparation (Correa et al., 2005), in other words the ability to orient attention in time implicates synchronization between expectations of target occurrence (perceptual aspect) and motor output or response (motor aspect). In the literature, it has long been established that warning signals improve reaction times to targets, and optimize performance by anticipating the moment at which the target will appear.

To study the notion of processing speed and temporal preparation, we have chosen alertness from the various component of attention, thinking that it could serve as biomarker of time pressure and mental effort. It is a fundamental component that mobilizes both vigilance and time expectancy (temporal preparation) of an upcoming event (W. Sturm et al. 1999; Walter Sturm and Willmes 2001; Clemens et al. 2011; Posner and Bois 1971). It includes two different analytical process (top-down), which participates in the deployment of attention in a context of temporal optimization of the action (preparation), and in a more intuitive way the regulatory (bottom-up) processes, which may facilitate (accelerate) stages of information

processing (Nobre & Coull, 2010).

In this context, we propose to study these two systems through an original multidimensional experimental protocol which allow us, by manipulating different variables, to extract imaging, behavioral and psychological data that we speculate sufficient to investigate our working hypothesis. We use motor imagery task to emphasize attentional resources and to see the effect of this attentional reinforcement on temporal processing. We propose, through a simple reaction time task, to vary time lengths (FPs) before the imperative stimuli which require a response in order to examine behavioral changes and to elucidate the way in which the brain controls attention following short temporal changes. The foreperiod is defined as a vigilant situation presented before the imperative stimulus and in which arousal increases relatively to its duration (Posner et Bois 199). It is generally used in reaction time tasks to optimize temporal preparation and consequently performance. Si it may constitute a suitable behavioral parameter that helps assessing the temporal processing in attentional tasks.

In the brain, we have focused our interest on a specific network including three brain regions: anterior insula (AI), anterior cingulum cortex (ACC), and dorsolateral prefrontal cortex (DLPFC). We previously demonstrated in (Périn et al., 2010) the neural substrates of alertness involved key brain regions including especially the (DLPFC) and anterior cingulum cortex (ACC). Also, recently, others studies (Coste & Kleinschmidt, 2016; Sadaghiani & D'Esposito, 2015) have demonstrated that alertness is a fundamental function of the Cingulo operculum network in which anterior insula (AI) and anterior cingulate play a crucial role in the control of intrinsic alertness. In addition to the fundamental role of these three structures in the maintenance required by alertness, they have been demonstrated to have a major role in the control of timing in reaction time tasks. The DLPFC has been demonstrated to be responsible of the temporal preparation (Stuss et al., 2005; Vallesi, Mussoni, et al., 2007) the AI is known to intervene in time perception (Craig, 2002) and finally, it has been shown that the ACC facilitates temporal processing particularly during very brief intervals (Bertelson & Tisseyre, 1969; Niemi & Näätänen, 1981; Stuss et al., 2005). Also, these three regions share an architectural neural basis; the von economic neuros (VENs). These neurons are thought to be speed conducting giving the large axonal size of which they are characterized. The role of these neurons still unclear, they have been attributed an important role in the social domain especially in the speed of social decision-making during quick changing situations (Allman 2005)

Herein, we speculate that if the participants are mentally and intensively trained to react to target stimulus, we can increase the vigilance level (arousal) and speeding up temporal processing by increasing cerebral activity in the AI, ACC and DLPFC. When activity within these regions increase, the transfer of signals sent through the VENs would obviously increase and consequently accelerate information processing. Therefore, our main hypothesis is that mental training would reinforce alertness and modify the cortical excitability in specific brain regions responsible for the control of attention by enhancing dynamically, from a model of psychophysiological interaction, both top-down control system during extrinsic alertness through DLPFC—AI circuit and bottom-up system during intrinsic alertness through AI—ACC and AI—DLPFC circuits.

II) Method

1) Participants

39 healthy participants (20 females and 19 males) aged between 21 and 35 years old (Mean = 27.5; sd = 4.50) with no known history of neurological, psychiatric or sensorimotor disorders were recruited. All participants were right handed, as assessed by the Edinburgh inventory for right-handedness. In this study, we compare two groups: a group named wMT "with mental training" who did the visuo-motor imagery before the real physical task (n=19) and a group named "woMT "without mental training" (n=20).

2) Neuropsychological assessment

Both groups (wMT and woMT) underwent a neuropsychological battery including three tests that have been selected according to their cognitive domains. 1) Concentration and speed capacities (sustained attention and visual scanning respectively) measured with the d2 test (Bates & Lemay, 2004) ; the score measured with d2 represents the percentage of errors calculated following this formulae F%= (100*F)/GZ where F is the number of errors (number of omissions + number of "d" that should not have been circled) and GZ is the number of circled items (Steinborn, Langner, Flehmig, & Huestegge, 2018) 2) Executive functions, selective attention, and cognitive inhibition were measured with the stroop test (Words and Color) (Golden, 1976)3) ; the time to read colors names printed in incongruent colored ink has been measured ; The trial making test "TMT" (parts A & B) provides information on

visual search, scanning and mental flexibility (Pena-Casanova et al., 2009; Tombaugh, 2004) ; the score on each part represents the amount of time (in seconds) required to join in ascending order digits (part A) and digits + letters (part B)(Corrigan & Hinkeldey, 1987; Gaudino, Geisler, & Squires, 1995; Golden, 1976). All the participants had to complete the three tests before and after the real physical task. Scores were compared using a paired t test within each group.

3) fMRI paradigm

The paradigm consists of 2 alertness conditions in which participants were asked to focus their attention and squeeze the handgrip with the left hand as quickly as possible when a target appeared (white square) respecting the required force level (low, medium and high). The purpose of using the left hand is to incite participants to produce more mental effort during mental training. The three levels of forces are chosen to make the task less monotonous, requiring participants to prepare for the task without producing reflex (automatic) responses and to stay focused on the whole duration of the task.

During the intrinsic alertness condition, participants have no information about the occurrence of the imperative stimulus (target). In the extrinsic alertness condition, a black screen was presented to act as a temporal cue before the target. Task instructions were displayed on the screen at the beginning of each alertness condition (figure 15). In both conditions (intrinsic and extrinsic), each trial included a central fixation cross on a black screen (5 degrees visual field). A sensorimotor control task was used in which the participants had to perform a voluntary self-paced handgrip squeeze with a frequency around 1 Hz while watching passively a fast (10 Hz) flickering white square, avoiding synchronization with the squeezing.

The target (white square) was displayed with different randomized fore-periods (FPs). The FP represents, according to (Posner and Bois 1971), a vigilance situation where alertness must be increased rapidly and maintained over a relatively brief interval. In more specific terms, it is considered as the waiting time interval varying within a fixed range of values which allows the subject to install a preparation (during intrinsic alertness) and the preparatory interval between a warning cue and the imperative stimulus (during extrinsic alertness). FP Durations for intrinsic alertness were: 250, 280, and 310ms. Those for extrinsic alertness were: 650, 680 and 710ms.

The experimental task was assessed with a block design and the order of the blocs was randomized through the three conditions. FPs were equally distributed and randomly presented within eight blocks of trials. The visuo-motor imagery task was performed, as a mental training task, in the scanner by half of participants before the real physical task (wMT group). They were told to execute exactly the same task but mentally by imaging squeezing the handgrip (without motor output). Both tasks last 30 minutes (2 x 15 minutes). The rest of participants did not perform the visuo-motor imagery task (woMT group). ”

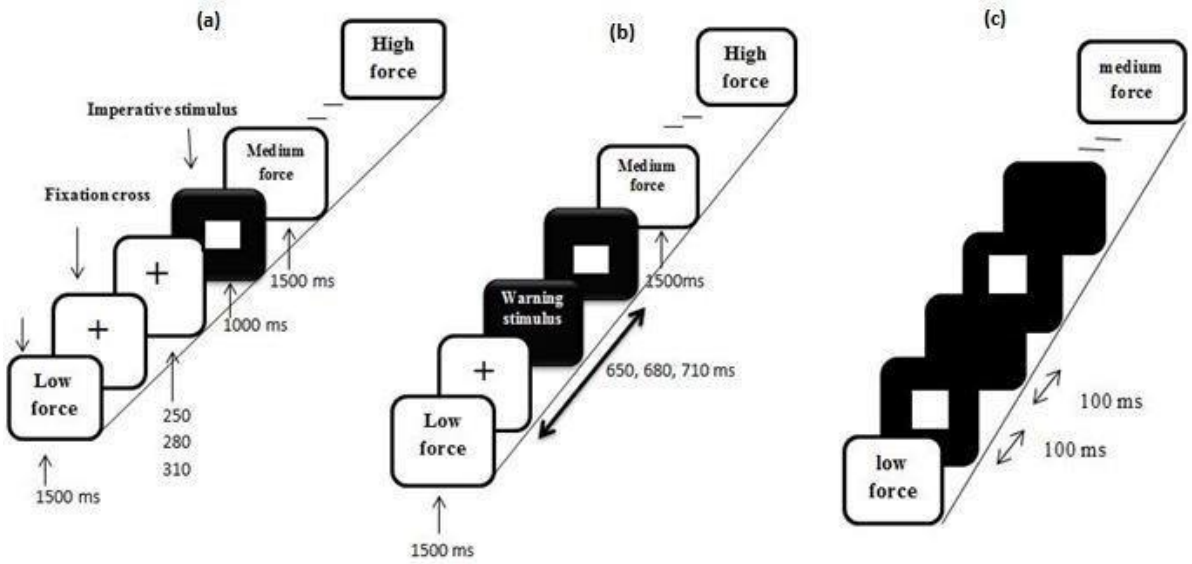


Figure 15: a) Extrinsic condition: participants had to respond to a white square. The warning stimulus was displayed during 400 ms and preceded the imperative stimulus with a varying fore-periods “FPs”. b) intrinsic condition: Participants had to respond to a white square. A central fixation cross was displayed permanently and c): Subjects had to respond to a flashing square every 100 ms. Instruction (concentrate and squeeze the handle with the required force level) was delivered at the beginning of each new condition

4) MR data acquisition:

Neuroimaging data were acquired at Pontoise Hospital Centre on 1.5-Tesla, whole-body MRI system equipped with Sigma head volume coil (General Electric Medical System, Milwaukee, WI). Functional images with Blood-Oxygen-Level Dependent (BOLD) contrast enhancement were acquired for each participant. Single-shot echo-planar images (EPIs) acquired using a typical T2*-weighted gradient-echo sequence. A total of 310 EPI volumes x 2 with no gap (TR/TE = 3000/44 ms; flip angle = 90 degrees; matrix = 64*64; FOV= 240x240 mm2) were

obtained for the experimental runs, whole brain volumes compromising 44, axial slices with 3.75-mm thickness (isotropic voxel volume = 52.7 mm^3). For structural images, conventional T1-weighed 3D imaging fast spoiled gradient recall - brain volume (FSPGR) BRAVO sequence was employed with these parameters, matrix: 256x256; flip angle: 12 degrees; TR/TE: 8.6/3.3 ms; FOV: 240x240 mm2; 168 slices, 1 mm^3 isotropic voxel resolution.

5) Image pre-processing

Image pre-processing was performed using Statistical Parametric Mapping (SPM12) software (Wellcome Centre for Human Neuroimaging, University College London,UK; http://www.fil.ion.ucl.ac.uk/spm). EPI volumes were corrected to adjust for within-volume time differences and realigned with the first volume to correct for head movements. Functional scans were then co-registred with the 3D structural image and spatially normalized against the standard, stereotactic space of the MNI template. Spatial smoothing was performed with 8mm Gaussian kernel full width at the half maximum (FWHM).

6) SPM analyses

BOLD hemodynamic responses were modelled as a box-car function convolved with a synthetic hemodynamic response function. The motion parameters were included in the General Linear Model (GLM) as regressors to correct the movement. A single-subject, fixed-effect model was created for each individual participant in order to perform the based-conditions random-effect analysis The results presented are from the image acquisition during performance of the real physical task thresholded at $p<0.05$ Family-wise error (FWE) corrected for multiple comparisons.

To ensure that the all participants recruited the intrinsic and extrinsic alertness system regardless of mental training, we have reproduced, using a one-sample t test, the contrasts published in (Perrin et al. 2010):“Intrinsic alertness task > sensorimotor task” and “extrinsic alertness task > intrinsic alertness”. The sensorimotor condition has been used as control of the intrinsic alertness and the intrinsic alertness represents the control of the phasic alertness. For each contrast all participants were regrouped (n=39) to make sure that both alertness systems are activated despite the presence of different force level contractions required in the task. These two contrasts have served as a base on which all next analysis were carried out. Then, we performed, a two-sample t test, to compare the differences between the groups: “wMT” > “woMT”.

7) Psychophysiological interaction (PPI) analysis

We perform an effective connectivity analysis to explicitly examine the influence that one neural system exerts over another, either at a synaptic (i.e. synaptic efficacy) or at a population level (Friston et al., 1997). The effective connectivity must be understood as the experiment- and time-dependent, simplest possible circuit diagram that would replicate the observed timing relationships between recorded neurons. To examine the effective connectivity between the AI, ACC and DLPFC regions, a psychophysiological interaction (PPI) analysis was performed to investigate interactions among these three brain regions. A PPI analysis tests the hypothesis that activity in one brain area can be explained by the interaction between the presence of a cognitive process (attentional reinforcement) and activity in another region of the brain. We predicted that the activity of a source region will covary with the activity of target regions. On the basis of anatomical connections, we performed an effective connectivity analysis to determine the effects of mental training on AI-ACC-DLPFC circuits. Through this analysis, we hypothesize that effective connectivity between "AI→DLPFC", "AI→ACC" (during intrinsic alertness condition) and "DLPFC→ACC" (during extrinsic condition), would increase after mental training. The AI was chosen as a seed (source) region in the intrinsic alertness condition. In extrinsic condition, DLPFC was chosen as seed region which exert a top down control on ACC.

8) Statistical analyses

Trials in which the RT was longer than 1000 ms or shorter than 100 ms were excluded from the analysis. Statistical analysis was performed in Statistica® software (version 13.3) and significance threshold was set to $p<0.05$. A two-way analysis of variance (ANOVA) groups ["wMT" vs "woMT"] vs task [intrinsic vs extrinsic] was carried out to examine effects of mental training on alertness. Then, another two-way ANOVA was conducted separately for each modality with fore-periods ["650 vs 680 vs 710" for extrinsic condition and "250 vs 280 vs 310" for intrinsic condition] x groups ["wMT" vs "woMT"] in order to examine effects of mental training on temporal processing. When the ANOVA indicated significant main effects and/or interactions, Bonferroni post-hoc comparisons were used in order to compensate for the family-wise-error in multiple comparisons for each group of pair wise comparisons.

III) Results

1) Neuropsychological results

Within the "wMT" group, in the comparison "before/after the real physical task", we found significant differences for the three cognitive tests: With the d2 test (mean before mental training "F%"= 6.27, sd= 4.04, mean after mental training "F%"= 3.84, sd= 3.46, p=.009), and Stroop test (mean before mental training = 81.41s, sd=17.53, mean after mental training = 76.28s, sd=18.93, p=.005). Finally, with the TMT test, a significant difference was found for the second part of the test (part B) (mean before mental training = 49.37s, sd=24.70, mean after mental training = 43.34s, sd=24.27, p=.02). No significant difference was observed within part A. Within the "woMT" group, no significant neuropsychological difference was found between before and after task completion.

2) Behavioral results

a) Anticipations

Anticipations have been measured within both groups in the whole task. Results show a significant interaction [group*task], *F (1.2) =51.57; p=.01*. Post hoc comparisons show increased anticipation rate during extrinsic condition compared to intrinsic condition within each group (wMT group: extrinsic condition: 11.69%, intrinsic condition 1.93% *p= .003;* woMT group: extrinsic condition: 3.24%, intrinsic condition 2.31%; *p=.01*. When comparing the extrinsic condition between the two groups, the anticipation rate was significantly higher in the "wMT" group (11.69%) than in the "woMT" group (3.24%) ***p=.009*** which confirms the acceleration of the response during the extrinsic alertness after mental training No anticipation rate difference was found during the intrinsic alertness.

b) Reaction times (RTs)

RTs have been measured within both groups in the whole task without separating FPs. ANOVA [task * groups] revealed a significant interaction; F (1, 23) =12.46, *p=.0004*. Post hoc comparisons showed significant RTs differences between the two groups during both alertness tasks. *For intrinsic alertness condition;* "woMT" group: mean = 400.28, sd=116.61, "wMT": mean =379.29, sd=101.30) (*p=.0001)*. For extrinsic alertness condition; "woMT": mean =388.53, sd=130.07, "wMT" mean =345.23 sd=137.37) (p<.01). RTs were significantly shorter within "wMT" group in both alertness conditions.

c) Foreperiods (FPs

❖ Intrinsic alertness condition

Factorial ANOVA [FPs x groups] showed a significant interaction; F (2, 16) =3.04, p=.04 Post hoc comparisons showed, within "woMT" group, significant differences of RTs between the shortest FP (250ms) (*mean* = 405.87 sd= 129.52) and the longest FP (310ms) (*mean*=384.09, sd=99.33) *p=.001* and between FP (280ms) (*mean* = 402.64 sd= 117.77) and FP (310ms) (*mean*=384.09, sd=99.33) *p=.01*. No significant differences in "wMT" were observed. When comparing each single fore-period between the two groups, post hoc comparisons showed that RTs decreased significantly after mental training for shortest FPs (250ms) : "woMT" *mean* = 405.87, sd= 129.52 , "wMT" *mean* = 380.97, sd=105.46 *p=.008*. For FP (280ms): "woMT" (*mean* = 402.64 sd= 117.77), "wMT" *mean* = 374.15, sd=89.85 *p=.001*. No significant difference was found for the longest FP (310ms).

❖ Extrinsic alertness condition

Factorial ANOVA [FPs x groups] revealed a significant interaction; (F (2, 14) =3.1, p=.04). Post hoc comparisons showed within "woMT" group, a significant difference of RTs *p=.01* between the shortest FP (650ms) (*mean* = 415.37, sd= 140.25 and the longest FP (710ms) *mean*=393.66, sd=131.60*; no significant difference was observed between FP 680 and 710 ms. Within* "wMT" group, no significant differences was observed between the three FPs. RT values for 650 ms FP have become shorter and similar to those of 680 and 710 ms. When comparing between the two groups each fore-period, post hoc comparisons showed that RTs decreased significantly (*p=.001)* after mental training for the shortest FP (650ms); "woMT" *mean* = 415.37, sd= 130.79, "wMT" *mean* = 377.49, sd=147.91. No difference was found for the longest FP (680ms and 710ms).

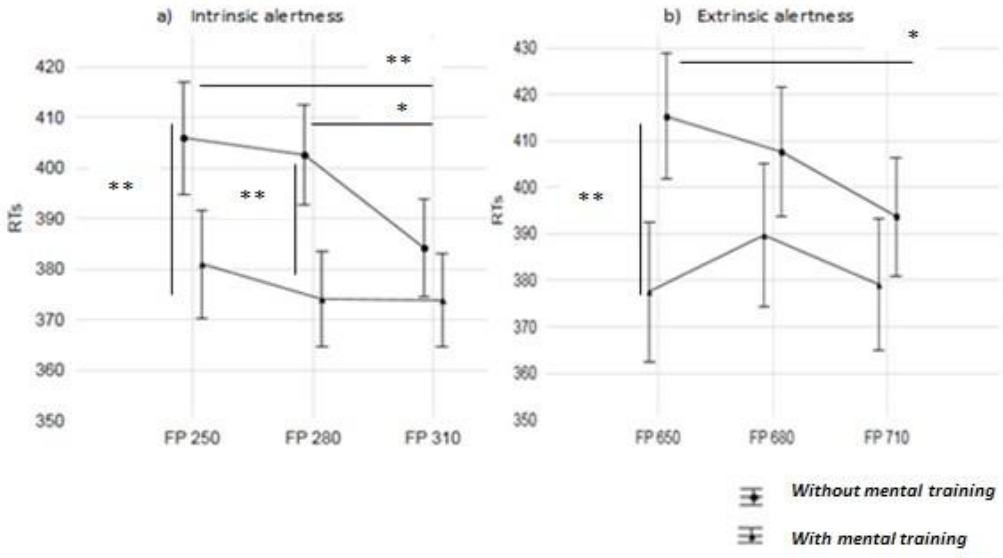


Figure 16: *Results of ANOVA [Fore-periods *groups] during intrinsic (a) and extrinsic (b) alertness tasks. **: p<0.01; *: p<0.05*

3) Imaging results

In the intrinsic alertness task > sensorimotor task contrast (n=39), increased brain activity was mainly found within the right hemisphere in anterior insula, anterior cingulate (ACC), inferior parietal cortex (IPC), thalamus, dorsolateral prefrontal cortex (DLPFC) and inferior (IFG)) (*Table1*).

Regions	**Side**	**BA**	**x**	**y**	**z**	**t**	**P(FWE_corr)**
Insula	R	BA 13	45	-1	1	6.58	0.001
DLPFC	R	BA 46	9	50	27	5.17	0.007
IPC	R	BA 40	54	-28	25	4.94	0.007
ACC	R	BA 32	3	47	7	5.37	0.002
Thalamus	R		12	-10	4	4.93	0.007
IFG	R	BA 44	57	14	13	4.24	0.02

Table 1*: Brain activations for "Intrinsic alertness task > sensorimotor task" contrast. Results of a one-sample t-test of activated regions for the intrinsic alerting versus sensorimotor contrast. Regions; side (R/L); Brodman areas ; X, Y, Z: MNI coordinates, FWE-corrected p values (p<0.05).*

We observe in the extrinsic alertness task > intrinsic alertness task contrast (N=39) more bilateral activations within the left hemisphere in IPC, DLPFC and thalamus (*Table2*).

Regions	**side**	**BA**	**x**	**y**	**z**	**t**	**P(FWE_corr)**
insula	R	BA 13	42	11	4	4.28	0.04
IPC	R	BA 40	42	-46	43	5.49	0.0009
	L	BA 40	-42	-31	43	4.41	0.04
ACC	R	BA 32	12	26	25	4.53	0.03
DLPFC	R	BA 9	45	17	28	3.49	0.02
	L	BA 9	-51	8	28	4.53	0.04
Thalamus R	R		18	-19	1	4.78	0.005
			-24	-25	7	3.28	0.02

***Table 2**: Brain activations for the extrnsic Alertness Task > Intrinsic Alertness Task contrast Results of a one-sample t-test of activated regions for the phasic alerting versus intrinsic alerting contrast. Regions side (RL), MNI coordinates, FEW-corrected p values (p<0.05).*

In the contrast "wMT" > "woMT" (two-sample t-test), activations were significantly enhance for both alertness conditions. Within intrinsic alertness condition, activations were mainly increased in the right hemisphere: anterior insula (AI), anterior cingulate cortex (ACC), inferior parietal cortex (IPC), thalamus, dorsolateral prefrontal cortex (DLPFC) and Putamen. Within extrinsic alertness condition: similar activations were observed, notably bilateral in IPC and putamen (Table 1).

Regions	*Side*	*BA*	x	y	z	t	P(FWE_corr)
Intrinsic Alertness							
IPC	R	BA 40	42	-46	46	4.5	0.007
ACC	R	BA 32	6	26	-8	4.43	0.009
DLPFC	R	BA 46	45	26	22	4.92	0.004
insula	R	BA13	51	-43	19	5.61	0.001
Thalamus	R		15	-10	10	4.27	0.01
Putamen	R		27	2	7	3.88	0.03
Extrinsic Alertness							
ACC			6	44	-2	6.01	0.0004
IPC	R	BA 40	48	-37	37	3.97	0.01
-	L	BA 40	-57	-28	31	3.69	0.02
DLPFC	R	BA 46	42	35	19	4.82	0.001
insula	R	BA 13	42	41	1	5.07	0.006
thalamus	L		-3	-7	1	3.9	0.03
Putamen	L		-21	11	-5	5.29	0.001
-	R		30	-16	4	4.96	0.003

Table 3*: Results of two-sample t-test of activated regions for the intrinsic and extrinsic alerting contrast with mental training > without mental training ; Regions side (R/L), MNI coordinates, FWE-corrected (p<0.05).*

4) Effective connectivity results

During intrinsic alertness condition in the "wMT" group, results showed, significantly increased effective connectivity between AI (x: 39, y: 2, z: 10) and DLPFC (x: 51, y: 29, z: 31) *pFWE=.001* and between AI (39, y: 2, z: 10) and ACC (x: 9, y: 41, z: 7) *pFWE=.01* for the shortest FP (250ms). No increased effective connectivity was found for the longer FP (310ms). During extrinsic alertness condition, in the "wMT" group, results showed significantly increased effective connectivity between DLPFC (x: 57, y: 32, z: 19) and ACC (x: 3, y: 41, z: 7) *pFWE=.005* for shortest FP (650ms). No significant increased effective connectivity was found for longer FP (710ms).

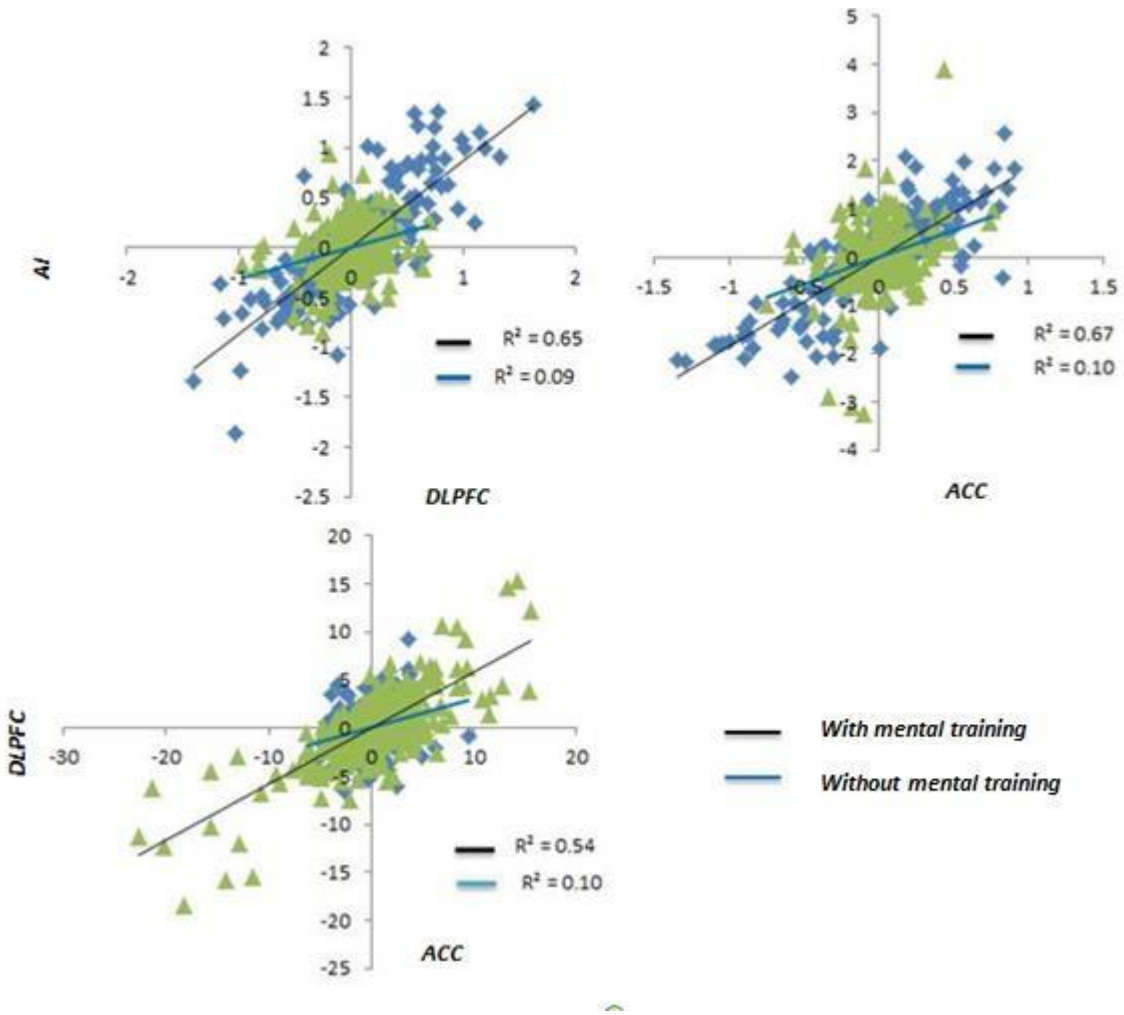


***Figure 17**: Results of the psycho-physiological interactions within "with mental training" group. Slopes found between AI-ACC, AI-DLPFC and DLPFC-ACC in the context "with/without mental training" are significantly different ($p<0.05$, FWE-corrected). PPI show, durin during intrinsic alertness condition, significant increased interaction in the right hemisphere between AI and DLPFC and between AI and ACC for 250ms FP. During extrinsic alertness condition, effective connectivity was significantly increased between DLPFC and ACC for the shortest FP (650ms). No significant difference was found within the "without mental training".*

IV) Discussion

Our study investigated whether attentional reinforcement induced by mental training could ameliorate temporal processing. To this end, we examined the potential interaction of alertness task with the FPs on RTs and this by using a variable-FP paradigm with three equiprobable FPs of 250, 280, 310 for intrinsic alertness and 650, 680, and 710ms for extrinsic alertness. Our results showed that mental training was successful in shortening RTs for the entire paradigm and provides evidence that a temporal deployment of attention by mental training, shifts the optimal response for preparation particularly to short time scales

and reinforces dynamically both top-down (extrinsic alertness) and bottom-up (intrinsic alertness) networks responsible for the control of attention.

1) Effect of variable FPs paradigm on RT

To begin with, our neuropsychological tests (Stroop, TMT and the d2) of attention show that performance has become better after mental training which means that processing speed capacities have become better. In addition, behavioral results provide clear evidence of FPs effect in intrinsic and extrinsic alertness. Within the "woMT" group, RTs are significantly shorter for long FPs. This result goes in line with many studies in which the warning stimulus is known to increase probability to respond at the prominent moment (Périn et al., 2010). Likewise for intrinsic alertness condition, RTs were shorter for longer FP (310 ms) relatively to (250 ms) and (280 ms). This result was not necessarily expected because intrinsic alertness does not engage a real process of preparation. This result goes with some other studies (Hackley et al., 2009; Kiesel, Miller, & Ulrich, 2007; Stahl & Rammsayer, 2005) in which accessory stimuli (in our case the cross presented with randomized FPs) still produce a benefit on RTs even though there is no explicit temporal preparation in this situation. In fact intrinsic alertness is associated more to "involuntary preparation" (JT T. Coull & Nobre, 2008) during which stimuli are presented continuously without informative cues. Temporal expectations are engaged incidentally as a consequent of the regular stimuli occurrence over time. These stimuli are controlled by the *involuntary attention* or "involuntary selection processes" (Berlyne, 1950) because they elicit involuntary surge of arousal. Involuntary attention is the capacity to allocate attention to novel and sudden stimuli and select unconsciously relevant from irrelevant stimuli; the pattern of physiological responses which is elicited by novel stimuli is variously named the orientation reaction, response, or reflex (Kahneman1973). Thus, during intrinsic alertness the FP effect would be originating from this involuntary selection process.

The FP effect has disappeared within the "wMT" group and no significant difference of RT was observed between the three FPs within both alertness conditions. When comparing separately each identical FP between the two groups, results show that RTs are shorter within "wMT" group for the shortest FP for both alertness conditions. These results reveal that attentional mental training helps participants to optimize their behavioral performance by shortening the time interval necessary for generating an optimal response. For longer FP, the

behavioral performance was maintained and performance efficiency remains the same and didn't improve with attentional training. This result can be explained by the fact that the state of readiness was optimal and participants could not go beyond their optimal performance regardless the presence or not of attentional reinforcement and that short FPs were more sensitive to arousal increase. Unexpectedly, this result is relevant for both alertness conditions, thing that leads us to assume that despite extrinsic and intrinsic alertness are two different systems, there would be a real common neural basis responsible for temporal processing.

2) Neural circuits subserving temporal processing

Our study provides evidence that temporal processing during alertness, whether intrinsic or extrinsic, is generated by the same neuronal basis following a coupled control "top down and bottom up" which depends on the nature of the task. In fact, our imaging data show that DLPFC, ACC and AI activity was broadly increased with mental training. In addition, PPI analysis highlights three neural circuits that were enhanced with mental training; The DLPFC-ACC (during extrinsic condition) and AI-ACC/AI-DLPFC (during intrinsic condition).

Actually, in the brain, the control of intrinsic alertness is related to autonomic nervous system or arousal mediated by noradrenergic and cholinergic systems originating from the ponto-mesencephalic part of the brainstem (Clemens et al., 2011; Gaspar et al., 1989; Jones, 2003; Robinson & Coyle, 1980). So, intrinsic alertness involves uncontrolled automatic mechanisms rather than voluntary control processes. It is considered as an adaptive system which includes intuition and unconscious mechanisms which evolve according to homeostatic changes. With attentional induction, these mechanisms seem to be adjusted much faster. This automatic adjustment appears to be more relevant for shorter FP in which the miniature vigilance bursts briefly and improves significantly the performance (Posner and Bois 1971). Furthermore, AI known to play a higher net causal outflow, helps to generate a bottom–up control involved in the transfer of fast control signals and stable maintenance of task mode and strategy (Cauda et al., 2011; Menon & Uddin, 2010). Despite the very short lapse of time (250ms) between the fixation cross (accessory stimulus) and the imperative stimulus (square), insula may help to facilitate temporal processing under attentional induction and this by providing relevant control signals to engage brain regions responsible for attention adjustment (ACC and DLPFC) (Menon & Uddin, 2010). This result is of great interest because it may constitute a theoretical basis for further studies on clinical population like multiple sclerosis who suffers the inability to sustain and orient attention to a given point, exhaustion and fatigue which are

more related to automatic physiological processes rather than higher order mechanisms.

Extrinsic alertness is related to high cognitive control (discrimination and selection processing during the temporal preparation). During this condition, the DLPFC is known to play a fundamental role in the organization and preparation of forthcoming actions. Based on information stored in the working memory (Pochon, 2001), the DLPFC exerts a top-down control on ACC when competition between responses increases and when inhibition of motor response is required (Dreher & Grafman, 2003). The DLPFC is responsible for maintaining a high-level of preparation during waiting interval, whereas, the ACC appears to be more directly involved in inhibition of responses, control monitoring and conflict resolution (Garavan, Ross, Murphy, Roche, & Stein, 2002). Via this top-down control, ACC may inhibit responses during delay period "the proactive inhibition" and prepares for the real motor execution at the right moment "the proponent response" (Narayanan & Laubach, 2009; Picard & Strick, 2001) This process may be related to two pools of antagonist neurons (excitatory and inhibitory) which interact continuously and synchronously during trials.

3) A possible implication of VENs in the speed of temporal-attentional processing

The VENs are particular neuros known to be implicated basically in intuition and rapidly adjusting behavior to quick changing social situations (Allman et al., 2005). Here in in this work we believe that they are not restricted to the social domain. The morphological characteristics, the large size and simple dendritic architecture and axon calibers of the VENs supports the conjecture that they are unique and faster conducting than the neighboring pyramids since conduction speed is proportional to axonal diameter. This characteristic allows them to have a critical role in temporal processing of information and puts a premium on the capacity to respond quickly to changing conditions and facilitates the rapid execution of decisions (Allman et al., 2005). Based on the fundamental characteristics of the VENs (speed processing and rapid conduction), we speculate with caution that they may constitute a neuronal basis of fast control signals not only for social changing situation but also for quick temporal pressure during the alertness tasks.

Since these neurons are speed conducting, richly innerving the AI, ACC, and DLPFC more in the right hemisphere and involved in adapting behavior to quick critical variations, we speculate with caution that they would intervene actively in adjusting responses to quick temporal changing during attentional tasks. Others investigations (at a microscopic level)

should be realized to consolidate this neural hypothesis because fMRI as an investigative technique does not support this type of hypothesis at a macroscopic level.

V) Conclusion

In conclusion, the present finding confirms the studies on classic FP effect and provides surprising and innovative neuropsychological insight on the temporal deployment of attention, suggesting that mental training of alertness using short training sessions could ameliorate the behavioral performance and reinforce the concentration. These findings strongly support the utility of using such protocol within clinical populations such multiple sclerosis known to experience difficulties in sustaining attention (vigilance) and temporally prepare for forthcoming actions, but also to disentangle the effects of mental and physical fatigue. The circuits investigated in this study could play the role of biomarker of central and peripheral fatigue in such populations.

Chapter 3/Study B: Effect of prolonged mental effort on sustained attention and temporal processing

Summary

This study deals with the question of whether FPs-related cognitive processes (expectancy) engaged during both alertness tasks modify when the mental effort increases over the time. The principle purpose of this work is to show, through the same protocol, that the neural circuits identified in the previous study may serve as markers of mental effort which must increase over the time. A neuropsychological test "the rate of perceived effort (RPE scale)" was determined at the end of the fMRI session in order to evaluate the subjective perceived exertion felt during the task. After a 30-minutes session including mental training plus real motor task, behavioral results showed, a significant cognitive performance decrement (increased reaction time) by the end of the session, specifically in the intrinsic alertness task and especially for short FPs (250/280ms) reflecting difficulties to deploy attention. This behavioral deterioration was markedly related to a decreased connectivity between AI-ACC and AI-DLPFC; The RPE scale shows that the motor imagery was more effortful and cognitively demanding compared to the motor task. We didn't observe difference within the extrinsic alertness task. We conclude that the behavioral components (FPs) and mental training may play a crucial role in temporal deployment of attention and would constitute psychological and neurological markers of mental effort or fatigue, notably through AI-ACC-DLPFC neural circuits.

I) Introduction

Cognitive performance in attentional tasks includes several aspects. The amount of resources that one is able to provide, the ability to sustain theses resources over time, the ability to focus and orient attention properly to the right target, and finally the ability to prepare for the action and react at the prominent moment. All these aspects require a huge mental effort to meet cognitive task demands. In fact, mental effort is generally experienced while performing any sort of cognitive task. It is described as spending energy and consequently experiencing a feeling of strain, a feeling that intensifies the harder a person tries" (Preston & Wegner, 2009). The resistance to intensive long periods of mental effort is assumed to deplete limited attentional resources (Grier et al., 2003; Smit et al., 2004b; Wright et al., 2008). The result of this resource depletion may lead to a state of mental fatigue, characterized by a failure to further exert appropriate bottom up and/or top-down dynamic control to maintain a stable allocation of cognitive resources to the task at hand (Lorist et al., 2000; Matthews & Desmond, 2002; Robert & Hockey, 1997)

Here in this work, through the same protocol we try investigate how performance fluctuates over the length of the alertness task (reaction time task) after a mental effort (motor imagery). We try to deal with the question of whether cognitive processes of timing and expectancy during an alertness task modify or decline with prolonged mental effort. More precisely, we try to see during an alertness task whether subject still benefit from the delay period presented before the target stimulus and could maintain an optimal temporal preparation when mental effort increases over time and how neural processes that underlie the temporal processing control preparedness and temporal expectancy and thus, performance.

The ability to attend selectively to a stimulus while simultaneously ignoring another (extrinsic alertness) is very different from the ability to maintain attention on a set of stimuli for prolonged periods of time (intrinsic alertness). (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994) indicate that "Vigilance represents the intensity and duration of attention while selective attention represents vigilance with preset sensory targets", so the temporal processing during both alertness would be controlled differently with increased mental effort. The beneficial effects of preparatory periods on performance can be seen when varying the level of temporal preparation. Thus by manipulating the temporal interval between the imperative stimulus and the preceded one called "foreperiod" (FP) (Risto Näätänen, 1971; M. I. and S. J. B. Posner, 1971). (RT) has been found to be shorter when The FP is long and

steadily increasing thereafter over time (Müller-Gethmann, Ulrich, & Rinkenauer, 2003). The decrease indicates that an optimal temporal preparation level is reached, and the increase is thought to reflect a difficulty in maintaining this preparedness as a consequence of the increasing subjective uncertainty about the moment of stimulus appearance (Los & Schut, 2008; Niemi & Näätänen, 1981). Here by employing a variable-FP design we examine whether indices of temporal preparation change over time along with global performance parameters. We try to deal with the question of whether neural processes that underlie the temporal deployment of attention contribute to the decline in preparedness and, thus, performance.

In the previous study, we have established a putative neural model that would intervene in temporal processing (AI-ACC-DLPFC). In fact, AI and ACC constitute the salience network which is responsible for switching between brain networks, as response to homeostatic changes, such the default mode network (DMN) and the central executive network (CEN); more specifically it is the AI, known as a key hub, which is modulates brain networks activity. These regions are strongly interconnected and richly connected to the noradrenergic system responsible for the control of arousal. The arousal system makes part of the autonomic nervous system in which the right hemisphere is preferentially involved in sympathetic activation and related more to respond to the unexpected stimuli and urgent behaviors (Craig, 2005; Rogers & Andrew, 2002; Wittling, 1995). The DLPFC is a cortical structure responsible for top-down control under high cognitive demands.

Taking together, we expect that intrinsic alertness would be more sensitive to mental fatigue compared to extrinsic alertness (decrease of arousal and increased RTs by the end of the task)). We suppose that anterior insula, known as key region of the salience network and assumed to generate bottom up signals to switch between brain networks, would be sensitive to arousal changes and would be impaired by attentional fatigue. This, consequently, would have a negative effect on its fundamental role in switching between brain networks, and the DMN whose activity should cease during the cognitive task by command from the AI would still activated at late moments of the task.

Also, we hypothesize, by manipulating FPs that attentional fatigue would not impair temporal preparation during extrinsic alertness and subjects still benefit from the warning stimulus to maintain optimal performance. However during intrinsic alertness, temporal readiness would deteriorate since for brief FPs there would be a relatively less precise time estimation which

might have made it more sensitive to cognitive fatigue at late critical moments.

To examine the working hypothesis, half of participants performed a mental training task (15') (mental training group wMT) to explicitly reinforce the flow and the cognitive load. Then, the same group performed the real task (15'). The rest of participants performed only the real physical task. Since mental training induced by motor imagery includes a strong cognitive content (Driskell, Copper, & Moran, 1994; Feltz & Landers, 2016; Yue & Cole, 1992), we expect for Wmt group a decrease in attentional resources by the end of the physical task resulting in mental fatigue state

II) Method

1) Participants

The same population 39 healthy participants (20 females and 19 males) aged between 21 and 35 years old (Mean = 27.5; sd = 4.50) executed the same alertness task in fMRI. They were asked to focus their attention and squeeze the handgrip with the left hand as quickly as possible when a target appeared (White Square). The whole population was divided into two groups: a group named wMT "with mental training" who did the visuo-motor imagery before the real physical task (n=19) and a group named "woMT "without mental training" (n=20).

2) Rating of perceived exertion scale

The Rating of perceived exertion (RPE) was determined at the end of the each fMRI physical and imagery run. The RPE scale allows giving the perceived exertion felt during the task which is defined as "the feeling of how heavy, strenuous and laborious exercise is" (Borg, 1962). This test allows participants to give a subjective intensity of effort, strain or discomfort, rating for the task. It consists of a 20-point scale ranging from 6 (very, very light) to 20 (very, very hard). The RPE scale is a reliable indicator of physical discomfort; it measures the amount of effort perceived by the subject during the task, sounds psychometric properties, and is strongly correlated with psychological measures of exertion (Pageaux, 2016). A Pearson khi square test was used to compare the RPE responses between the two.

3) Statistical analyses

Reaction times (RTs) were extracted for the two alertness conditions (intrinsic and phasic) using Acknowledge software (version 4.2) and E-prime (version 2.0.8.22) respectively. Analysis of variance (ANOVA with repeated measures groups [wMT vs woMT] x task period [early vs late], was carried out separately within each alertness task. Then, another ANOVA with repeated measures was carried out within groups [wMT vs woMT] x fore-periods [“650 vs 680 vs 710” for extrinsic condition and “250 vs 280 vs 310” for intrinsic condition] x task period [“early” vs “late”] in order to examine effects of increased mental effort on temporal processing according to each alertness task. When the ANOVA indicated significant main effects and/or interactions, Bonferroni post-hoc comparisons were used in order to compensate for the family-wise-error in multiple comparisons for each group of pair wise comparisons.

4) MR data acquisition:

Neuroimaging data were acquired at Pontoise Hospital Centre on 1.5-Tesla, whole-body MRI system equipped with Sigma head volume coil (General Electric Medical System, Milwaukee, WI). Functional images with Blood-Oxygen-Level Dependent (BOLD) contrast enhancement were acquired for each participant. Single-shot echo-planar images (EPIs) acquired using a typical T2*-weighted gradient-echo sequence. A total of 310 EPI volumes x 2 with no gap (TR/TE = 3000/44 ms; flip angle = 90 degrees; matrix = 64*64; FOV= 240x240 mm2) were obtained for the experimental runs, whole brain volumes compromising 44, axial slices with 3.75-mm thickness (isotropic voxel volume = 52.7 mm^3). For structural images, conventional T1-weighed 3D imaging fast spoiled gradient recall - brain volume (FSPGR) BRAVO sequence was employed with these parameters, matrix: 256x256; flip angle: 12 degrees; TR/TE: 8.6/3.3 ms; FOV: 240x240 mm2; 168 slices, 1 mm^3 isotropic voxel resolution.

5) Image pre-processing

Image pre-processing was performed using Statistical Parametric Mapping (SPM12) software (Wellcome Centre for Human Neuroimaging, University College London,UK; http://www.fil.ion.ucl.ac.uk/spm). EPI volumes were corrected to adjust for within-volume time differences and realigned with the first volume to correct for head movements. Functional scans were then co-registred with the 3D structural image and spatially normalized against the standard, stereotactic space of the MNI template. Spatial smoothing was

performed with 8mm Gaussian kernel full width at the half maximum (FWHM).

6) SPM analysis

BOLD hemodynamic responses were modelled as a box-car function convolved with a synthetic hemodynamic response function. The motion parameters were included in the General Linear Model (GLM) as regressors to correct the movement. A single-subject, fixed-effect model was created for each individual participant in order to perform the based-conditions random-effect analysis The results presented are from the image acquisition during performance of the real physical task thresholded at $p<0.05$ Family-wise error (FWE) corrected for multiple comparisons.

We conducted a first analysis within both groups in which we compare early period of the task (first bloc) and the late period (last bloc) of the motor alertness task. Through this analysis we try to investigate globally neural changes during intrinsic and extrinsic alertness under prolonged mental effort, potentially attentional fatigue. Then, following behavioral analysis, we examine the effect of prolonged mental effort on temporal aspects (FPs), we conduct the same analysis but by separating the FPs.

7) Psychophysiological interaction (PPI) analysis

Here following behavioral results we performed a PPI analysis to examine the effective connectivity between the AI-ACC and AI-DLPFC regions during intrinsic alertness and within “”wMT” group in which we expect a mental fatigue effect. These (PPI) analyses were conducted according to FP variable to investigate interactions among these brain regions and to determine the effects of prolonged mental effort on attentional temporal processing. Through this analysis, we hypothesize that effective connectivity between “AI→DLPFC”, “AI→ACC” (during intrinsic alertness condition) would decrease by the end of the task. The AI was chosen as a seed (source) region in the intrinsic alertness condition since it is responsible for generating bottom up signals and richly connected to ACC and DLPFC.

III) Results

1) Behavioral results

a) RPE

Rating of Perceived Exertion scale results showed that for the woMT group "group without mental effort", responses were scattered between light (6 responses), fairly light (9 responses) and hard (4 responses). For the wMT "group with mental effort", the majority answered very hard (12 responses) and the rest answered hard (6 responses) and light (2 responses). The chi2 Pearson test showed that there is a significant difference between the two groups (chi2 =23.38; df=3; p = 0.00003).

b) RTs

Results of ANOVA group [wMT vs woMT] * task period [Early vs Late] showed that performing a sustained alertness task preceded by mental training elicited a significant main effect of mental effort mainly in intrinsic alertness task F (1, 1320) =14.44, p=.00001. No significant effect was seen in extrinsic alertness. Post-hoc comparisons showed significant differences of reaction time between the early and the late period (Mean block early = 401.61, sd = 130.83and mean block late = 440.14, sd = 149.02) P = 0.0001 only in intrinsic alertness. No significant differences were observed in woMT group.

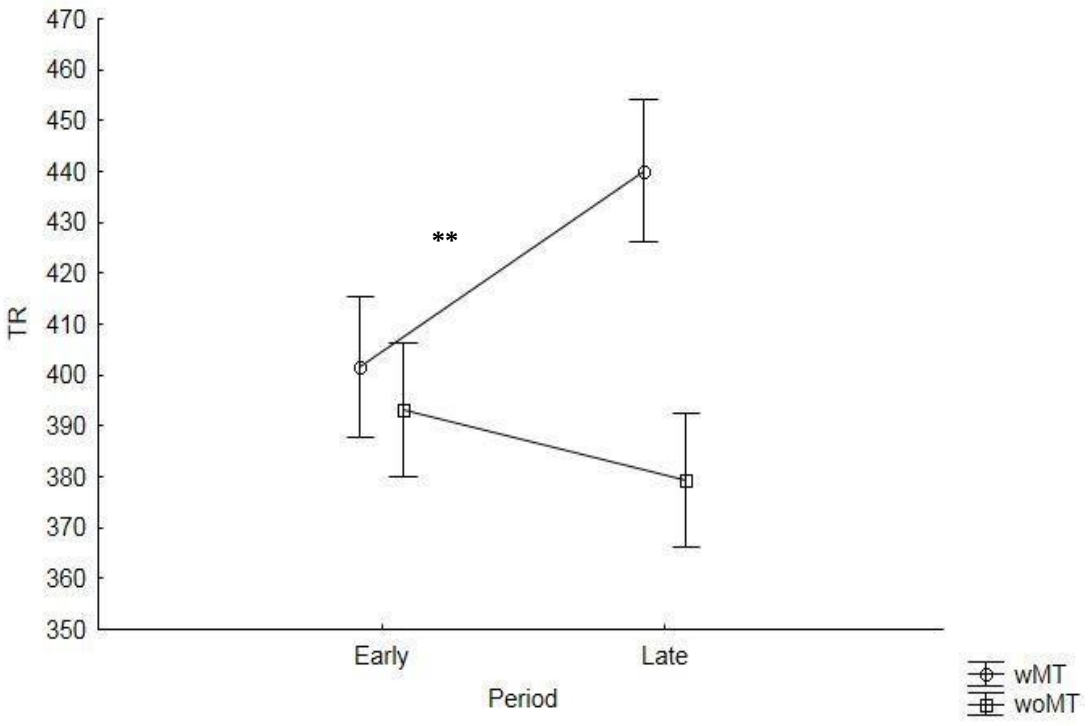


***Figure 18**: Results of ANOVA [Groups *Task period] during intrinsic alertness task.*

***: p<0.01.No significant effect was seen during extrinsic alertness task.*

For intrinsic alertness task, ANOVA FPs [250 vs 280 vs 310ms] * Task Period [Early vs Late] shows significant main effect of mental effort mainly F (2, 617) =3.48, p=.03. Post-hoc comparisons showed significant differences of reaction time between the early and the late period for both 250ms FP (Mean early period = 403.17, sd =137.22. and mean late period = 466.63, sd = 161.36) P = 0.001 and 280 ms FP (Mean early period = 398.70, sd=136.39. and mean late period = 454.01, sd = 145.40) P=.004. No significant difference was observed for 310ms FP. In extrinsic alertness, ANOVA shows no significant effect of foreperiod.

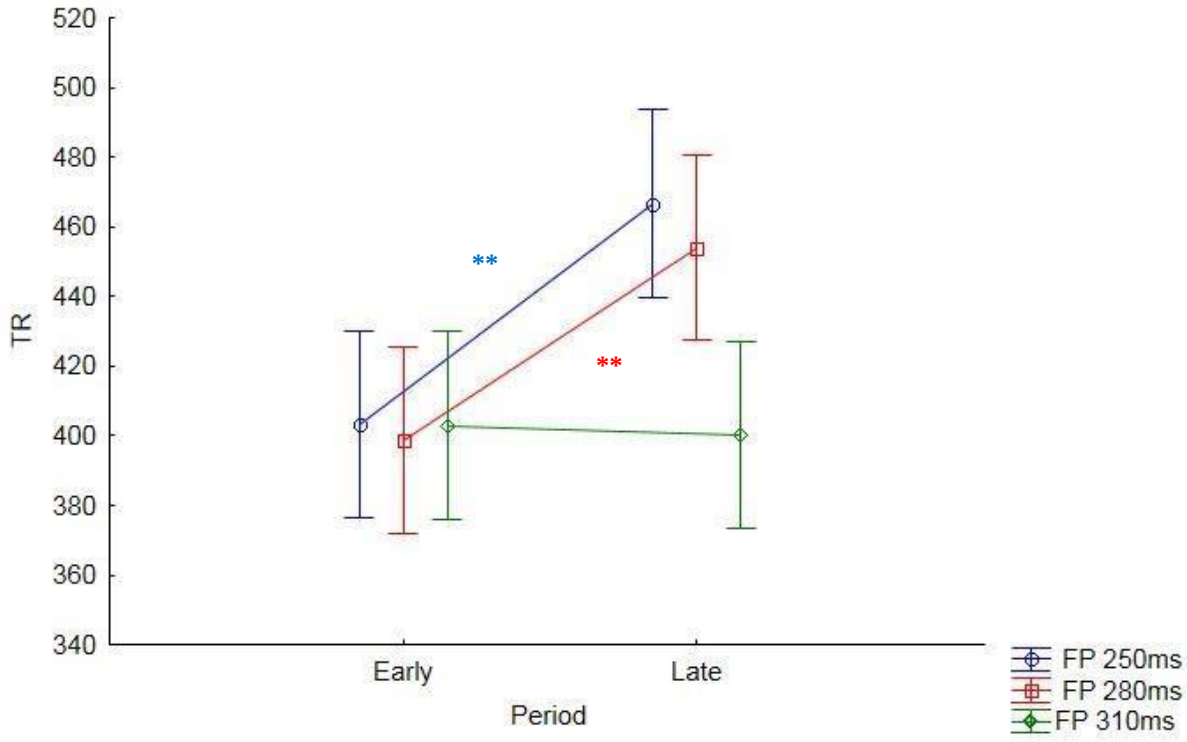


***Figure 19**: Results of ANOVA [FPs *Task period] for wMT group during intrinsic alertness task.*

2) Imaging results

When comparing the late period with the early period of the task within the group who did the mental training task first ("wMT"), the extrinsic task showed significant activation only in the dorsolateral prefrontal cortex (BA 9/46), insula and thalamus in the left hemisphere. Significant deactivations were observed in the intrinsic task within posterior cingulate, DLPFC, superior and medial frontal gyrus (SFG/MeFG), inferior parietal cortex and precuneus.

Regions	side	BA	x	y	z	t	P(FWE_corr)
Cingulate Gyrus	R	24	3	-1	31	4.21	0.02
Superior Frontal Gyrus	R	10	27	47	22	4.04	0.02
DLPFC	R	9	33	38	37	2.98	0.03
Insula	R	13	39	16	8	3.18	0.02
Medial Frontal Gyrus	R	6	9	-7	61	3.7	0.02
Precuneus	L	7	-18	-67	37	3.62	0.02
Precuneus	R	7	6	-43	52	3.18	0.03
IPC	R	40	39	40	49	3.30	0.03

***Table 4**: Brain deactivations for the late period>early period contrast in intrinsic alertness task within wMT group; Regions, side (R/L), MNI coordinates, FDR-corrected p values p<0.05.*

Regions	side	BA	x	y	z	t	P(FWE_corr)
DLPFC	L	BA 46	-42	32	16	5.12	0.002
		BA 9	-42	8	31	4.97	0.003
Insula	L	BA 13	-51	-31	19	4.74	0.001
Thalamus	L		-24	-22	1	3.68	0.04

***Tableau 5**: Brain activations for the late period>early period contrast in extrinsic alertness task within wMT group; Regions side (R/L), MNI coordinates, FEW-corrected p values p<0.05.*

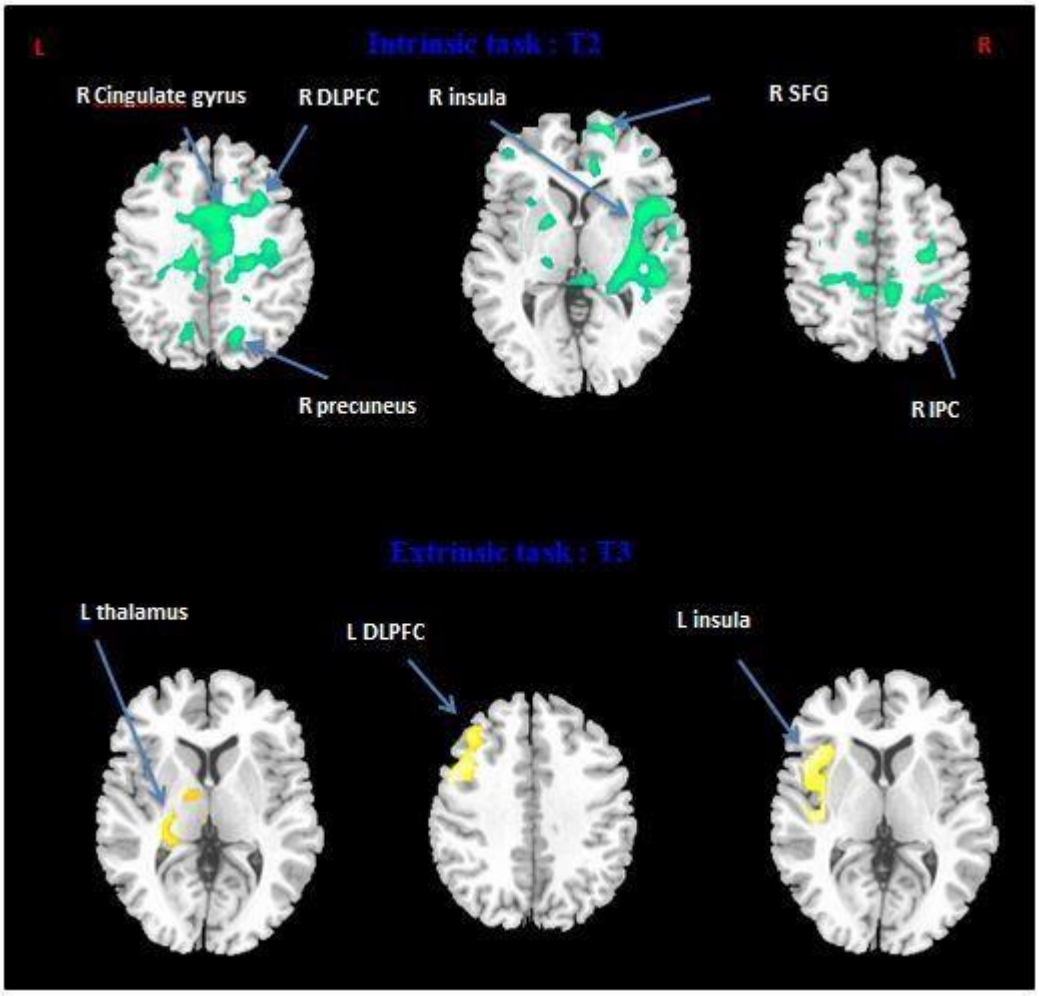


***Figure 20**: Brain areas maps, associated with "Late period> early period" contrast in wMT group. Results showed significant deactivations within intrinsic alertness especially in the right hemisphere (PCC, precuneus, SFG, insula and IPC. However, in extrinsic task, significant activations were observed in the left hemisphere DLPFC, thalamus and insula. The resulting activations were thresholded at FWE-corrected p values (p<0.05)*

When comparing Late period> early period for short FPs (250/280ms) during intrinsic task within the group who did the mental training task first ("wMT"), results show significant deactivation of our regions of interest (anterior insula (AI), anterior cingulate (ACC) and dorsolateral prefrontal cortex (DLPFC)) (table3).

Regions	side	BA	x	y	z	t	P(FWE_corr)
Intrinsic alertness							
DLPFC	R	9	30	35	37	3.04	0.03
ACC	R	32	3	44	7	3.39	0.02
AI	R		39	-43	19	2.94	0.04

Table 6*: Brain deactivations of regions of interest for the late period>early period contrast within wMT group" during intrinsic alertness (250 and 280 ms FPs). Regions, side (R/L), MNI coordinates, FDR-corrected p values p<0.05.*

3) Effective connectivity results

During intrinsic alertness condition in the "wMT" group, results showed significantly decreased effective connectivity by the end of the task between AI and DLPFC and between AI and ACC for the shortest FP (250/280 ms). No effective connectivity changes were found for the longer FP (310ms).

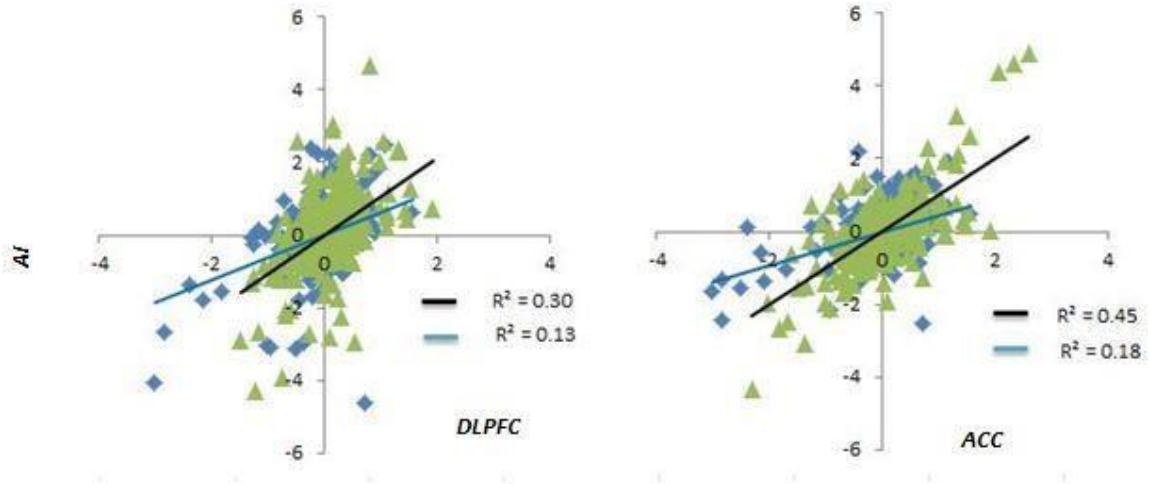


Figure 21: Results of the psycho-physiological interactions within "with mental training" group. Slopes found between AI-ACC, AI-DLPFC are significantly different (p<0.05, FWE-corrected). PPI show, during intrinsic alertness task and by the end of the task, significant decreased interaction in the right hemisphere between AI and DLPFC and between AI and ACC for 250/280ms FP.

IV) Discussion

The main objective of this study was to examine within healthy young participants the effects of induced mental effort (potentially cognitive fatigue) on specific brain regions and circuits by activating both intrinsic and extrinsic alertness systems. We examined as well the effect of increased mental effort on temporal deployment of attention by manipulating foreperiods during both intrinsic and extrinsic alertness.

1) Mental fatigue related neural and behavioral changes during extrinsic and intrinsic alertness

Our results revealed significant associations between behavioral performance decline and brain activation in the intrinsic alertness network. After mental training task, larger RT increase was observed from the early to the last period of the physical motor task in addition to significant deactivations in a large network comprising the dorsolateral prefrontal cortex, medial/superior frontal cortex, cingulate gyrus, precuneus, inferior parietal cortex and anterior insula. Some of these areas make part of the default mode network (PCC, precuneus and medial frontal cortex (MeFC)) and some others of central executive network (DLPFC) in addition to the anterior insula (AI). Normally, when a salient stimulus appears, the activation of the default mode network should cease, and the central executive network should be activated to handle the stimulus (Menon & Uddin, 2010). This functioning is mediated by the anterior insula which represents a hub in switching between the DMN and the CEN (Vinod Menon 2010). In our study when mental effort increases as time goes on, fatigue settles by the end of the task (increased RTs), consequently, CEN activity was decreased and DMN deactivation was accentuated. This can be interpreted by the inability of the anterior insula to efficiently imbalance between the two networks to handle a good cognitive performance. In fact, the intrinsic alertness task represents a simple repetitive detection task which engages a cognitive control of arousal and vigilance. sustaining attention to simple, repetitive tasks is perceived as effortful and highly cognitively demanding, inducing subjective strain or even ‘fatigue’ over time (Grier et al., 2003; Szalma et al., 2004; Warm, Parasuraman, & Matthews, 2008), difficulties in maintaining high performance levels directly result from a depletion of attentional resources that occurs with the continuous allocation of attention (Helton & Warm, 2008; Smit et al., 2004b). During extrinsic alertness task, no significant decline in

performance was observed within "woMT" group when comparing the early to the late period. However, significant activations within the left hemisphere in the dorsolateral prefrontal cortex (area 9/46), thalamus as well as the insula were detected form the beginning to the end of the task. Furthermore, no right inferior frontal or parietal areas changes were observed. This finding is congruent with results of (coull 1998) who found fatigue effects exclusively in the simple detection task and not for the selective task in which activity in the right hemisphere was preserved across the run. In fact, in contrast to the intrinsic task, the extrinsic task requires that activity in these regions (in the right hemisphere) be maintained as with increased mental effort (JT et al., 1998). Our findings are compatible with the results of (Demeter et al., 2011) in showing that even preserved right DLPFC function under conditions of mental effort 'potentially fatigue' is insufficient to sustain good performance. The extra cognitive demand of the phasic task leaded to recruit regions in the left hemisphere that allow the subject to cope with the additional selectivity processing demands and counteract deficit normally would be seen in the right hemisphere, so the effortful top-down control is needed to "stay on the job," and help maintaining attention over time and enable an efficient processing of task-relevant information (Sarter et al., 2006; Stuss et al., 2005). Thus, more contribution of left thalamus and left prefrontal regions in the extrinsic task is a way to cope with task demands. We suggest that the use of a warning stimulus may have contributed to sustain performance, since a warning stimulus may somewhat compensate for performance decrement typically found in simple detection tasks (without WS) (Lisper, Melin, & Sjoden, 1973; Sanders, Wijnen, & van Arkel, 1982). This external stimulus provides additional stimulation that might help for maintaining performance (Hackley et al., 2009). Our results are in line with studies which postulate that tasks with warning stimuli are little demanding in contrast to simple detection tasks known to be more cognitively demanding and most require an active control of attention when the ask is prolonged in time. These studies demonstrate the high vulnerability of simple, monotonous tasks to mental fatigue (JT et al., 1998; Langner, Steinborn, Chatterjee, Sturm, & Willmes, 2010)

2) Neural changes and performance decrements related to FPs variable design

Here, our findings show that when comparing separately RTs during FPs between the early and the late period of the task within "Wmt" group, results show that RTs increased significantly for the shortest FPs only during intrinsic alertness (both 250 and 280ms).

We suggest that it may be the timing under temporal uncertainty produced by short FPs and the efficiency of processing stimulus information because of the *decrease of arousal* that were

essentially affected by mental fatigue. In fact, during intrinsic alertness FPs are very short there is a relatively less precise time estimation which might have made it more sensitive to cognitive fatigue at late critical moments (Langner 2010). To be more explicit, the brief intervals preceding the imperative stimulus are not considered as temporal preparation for action but an implicit expectation that was implemented over time. We cannot talk about time uncertainty or preparation per se but about a short vigilant situation which we assume more sensitive to arousal changes; it may help to detect properly the target in normal situation, increase under mental training and decrease with mental fatigue.

One question remains to be answered: What processes in intrinsic alertness tasks performance are slowed by mental fatigue during short FP? To begin with, our fMRI results show decreased effective connectivity between AI→ACC, AI→DLPFC during intrinsic alertness (for 250 and 280 ms FPs). This may indicate that mental fatigue induced by increased mental effort may reduce responsiveness locally in the anterior insula and consequently reduces the quantity and the rapidity of signals sent to the ACC and DLPFC through the VENs (the von Economo neurons) and enables the insula to regulate attentional control. Efficient performance during intrinsic alertness tasks has been shown to involve bottom-up control within the right hemisphere to facilitate stimulus detection and to implicitly prepare the response in advance (Clemens et al., 2011; Frith & Done, 1986; Goodrich et al., 1989). This bottom-up control is generated by anterior insula which is strongly related to arousal system which in turn makes part of the autonomic nervous system. These bottom-up modulations are the most vulnerable to adaptive changes potentially mental fatigue which may affect all stages of information processing that receive modulatory bottom up input, from stimulus detection to response execution. Here in this study we cannot determine the exact locus of fatigue effects within a stage model of information processing, but we can speculate that it would be the conduction speed which was affected since AI-ACC-DLPFC network, that we assume responsible for temporal processing and conduction speed, was depleted for short FP. So, if arousal level was optimal, information processing would have been faster and the performance (RT) would have been maintained.

V) Conclusion

This study demonstrates that intrinsic alertness is more sensitive to mental fatigue and that mental effort processes during alertness tasks is assumed to be sub-served by both hemispheres and supported by a combination of stimulus-triggered (“bottom-up”) routine processing, and supervisory system (“top-down”) modulations. When fatigue arises, both

hemispheres behave in an inverse way during intrinsic and extrinsic task. For 'intrinsic alertness', right anterior insula which, play a prominent role in orchestring bottom-up capture of endogenous attention, arousal regulation and switching between networks was more sensitive to mental fatigue. Whereas, when discrimination demands increase in extrinsic alertness, left hemisphere has been further recruited by cognitive challenges to efficiency sustain attentional performance and cope with task demands. The most interesting finding is that this study confirms our previous findings in indicating that AI-ACC-DLPFC network may be responsible for temporal processing and conduction speed and would be a neural marker of mental fatigue.

General discussion: Study A+ B

The main objective of these two studies is to establish a neural model which may explain the timing aspect during attentional tasks and may serve as a biomarker of mental fatigue within several clinical populations. We manipulated the foreperiod as behavioral indicator of temporal processing. It represents a facet of global performance parameters that allow estimating the efficiency of temporal processing. We were able to implement through a multimodal protocol; a putative neural model in the right hemisphere that we suggest would be responsible for temporal processing of attention (AI, ACC, and DLPFC) and intervene actively in the speed conduction of information.

Without mental training the FP effect was observed during extrinsic alertness and unexpectedly intrinsic alertness task. In fact, temporal preparation is an integral part of any simple reaction time, in spite of the absence of an external stimulus during intrinsic alertness task, subjects still benefit from the brief FP presented with randomized intervals. We suggest that there was an "implicit preparation" that was implemented throughout the task (JT T. Coull & Nobre, 2008)

Under mental training induced by motor imagery, performance was improved for both alertness tasks for short FPs. no RTs changes were observed for long FPs. In fact, during motor imagery task, participants imagine responding to the imperative stimulus for 15 minutes without executing the motor act. We suggest that, during this period of inhibition of motor movement, the autonomic nervous system was permanently stimulated increasing by the fact the arousal level and facilitating the encoding of information at the most critical moments. Thus, the probability that the target would be displayed at an imperative moment has increased and consequently time uncertainty has diminished. These results are consistent with theoretical conception of Kahneman (1973) who considers that each sensory stimulus induces a sudden and momentary increase in the level of arousal, particularly through uncontrolled and adaptive mechanisms. Kahneman also assumes that arousal varies rapidly as an adaptive response to stimuli to which the organism is exposed. In addition, based on theoretical models which have focused on the comparison between the classic FP and the sequential FP effects, (Los & Van Den Heuvel, 2001) have associated each critical moment during a giving trial with a conditioned strength developed during the trials, the higher the conditioned strength at a critical moment, the shorter the RT will be if the imperative stimulus appears at that moment. It would be reasonable to assume that mental training has increased the "conditioned strength" during trials increasing consequently the predictability of target occurrence only for short FPs conversely to longer foreperiod in which temporal

readiness has remained unchanged and no RT improvement has been seen. This assumption goes also with the theoretical conception of (Los 2001) who consider that after some acquisition training, a conditioned response is developed and locked in time and obtains its peak at or about the moment the unconditioned stimulus is presented (Gallistel & Gibbon, 2000; Grossberg & Merrill, 1992; S. Roberts, 1998). The question remains why this improvement was seen only for short FPs and not for long ones? We may interpret our findings as a function of arousal modulation because the state of preparation is fully determined by the level of arousal. Arousal and conditioned strength are two dependent components (Vallesi & Shallice, 2007). In fact Vallesi and colleagues have established a theoretical model "dual process model" that may explain the "sequential effect" during reaction time tasks. According to this model, the higher the conditioned strength, the greater the level of participant's arousal would be. These authors assume that arousal tends to increase particularly during short FPs than long ones. Our findings are in line with the conceptualization of this model. Thus, under mental training, for longer FPs, arousal has already reached its optimal peak and could not exceed this optimal level however there were particularly short FPs which were more sensitive to arousal increase.

These behavioral assumptions are supported by the increased effective connectivity of AI-ACC, AI-DLPFC (intrinsic alertness) and DLPFC-ACC (extrinsic alertness). AI has been demonstrated, to intervene in arousal regulation (Craig, 2002; Critchley et al., 2002), it feeds the ACC with the necessary information which in turn spreads out these signals to the cortical regions. AI is also known to play a crucial role in time perception; it uses the representation of body states to perceive time (Craig, 2009). By temporally integrating transient signals from the body, it helps to produce "critical moments" and increase the perception of duration. We may speculate that in a given alertness reaction time task with variable FP intervals, anterior insula may integrate information on elapsed time after each response and sends it to the ACC-DLPFC, where it is then used, together with probability representations, for the preparatory timing of the allocation of attentional resources (Langner, 2010). The DLPFC, known as the locus of temporal readiness and has been found to be strongly active during foreperiods or "delay periods", increases predictability of target occurrence and cognitively prepares for the coming action. The ACC control and prepare the motor output. So it seems reasonable to assume that the temporal processing might be basically subserved by a functional AI-ACC-DLPFC system. Therefore, based on this proposal we suggest that mental training enhances anterior insula activity and the whole timing process behind.

After the motor imagery and by the end of the motor task arousal task engagement decreases and indicates mental fatigue state or resource depletion only for intrinsic and not for the extrinsic task. In fact, motor imagery used as a mental training represents a cognitively effortful task since participants reported (through the RPE scale) feeling less energetic after the imagery session than before. During the extrinsic alertness, the use of a warning stimulus may have contributed to the rather small performance decrement since it may somewhat compensate the time-related performance decline usually observed in non-cued alertness tasks (Lisper et al., 1973; Sanders et al., 1982). Also the WS provides additional stimulation of arousal which that might be beneficial for maintaining performance in monotonous tasks (Hackley et al., 2009). Conversely to extrinsic alertness, intrinsic alertness is known to be an effortful task which require much more energy and attentional resources which made it more sensitive to mental fatigue. In the brain we noticed an imbalance against different networks activity (DMN, SN, and EN). We attribute this malfunction particularly to anterior insula a well as the ACC which are known to be responsible for switching between brain networks. When fatigue sets in by the end of the physical task we have shown decreased AI-ACC connectivity. Probably this weakened connection has leaded to the decrease of anti-correlation between networks (DMN and CEN). This hypothesis of interaction between the different networks must be more investigated.

To investigate mental fatigue effect on purely temporal aspects (during intrinsic alertness task), we compared separating FPs between the early and the late period of the task. We noticed a mental fatigue effect only during short FP. In fact, we assume that, in general, mental fatigue induced by increased mental effort decreases arousal and conduction speed. For long FP, participants still have the possibility to benefit from this long waiting interval to temporally estimate the critical moment of target occurrence despite arousal decrease, conversely to short FP in which there is was less time estimation which is not sufficient to counteract arousal decrement. In the brain, we noticed decreased effective connectivity within AI-ACC and AI-DLPFC. In fact, if the temporal process is associated to conduction speed, there might be a direct influence of anterior insula on computational processes in cortical regions (ACC and DLPFC) via the von econmo neurons. In conclusion Mental fatigue affected basically anterior insula, consequently arousal decreases and all the functions associated with the AI have been affected (switching, time perception, bottom up control, control of arousal, conduction speed …). As a result performance declines.

Conclusions and Perspectives Study A+B

The aim of the study A is to develop a neural model that would help understanding the temporal processing of attention. Alertness was chosen to be explored in our protocol because it represents the simplest component from all attention components and considered to engage less computational mechanisms. As said in the introduction, it integrates simultaneously "vigilance" or "arousal" necessary for every attentional task, and "preparedness" or "readiness" which represents the ability to expect and prepare for action. The behavioral measure that we used to estimate temporal processing efficiency was the "Foreperiod" (FP). This latter represents the timing interval placed just before a target stimulus whose ultimate objective is to increase arousal and give participant the opportunity to estimate the critical moment of target occurrence. Through this study we were able to show that mental training induces a temporal deployment of attention and helps improving performance (decrease of reaction times) particularly when the target is preceded by a very short FP during both intrinsic and extrinsic alertness. We established a neural network comprising the anterior insula, anterior cingulate and dorsolateral prefrontal cortex). We suggest that this network would be responsible for temporal processing and that the von economo neurons (VENs), considered as a common neural architecture, would intervene in speeding the transfer of signals.

In the Study B we tried to examine the effects on prolonged mental effort on this putative neural model that we built trying to understand whether temporal aspects of attention change with increased mental effort. We found a fatigue effect (increased RT) by the end of the task only in intrinsic alertness and more precisely only for trials preceded by short FPs. Here, AI-ACC-DLEPC network appears to be depleted when mental effort perception increases (especially for short FP where we noticed fatigue effect).

The findings of both studies are of great interest because this is the first work that has emerged a neural model able to explain the timing aspects of attention which are less investigated in the literature. We were able to reduce the temporal scale of foreperiod in the order of milliseconds conversely to the scale on which (Valllesi et al) and (Los et al) had worked. They have established their theoretical models according to FP durations >1s. We assume that arousal modulation could be better evaluated for shorter FPs. So it would be advisable for future research as well as applications to employ a more particular protocol which includes a large FP scale design in which durations should be varied from very short to very long to better understand arousal modulation according to FP length. We propose for future studies to investigate the effect of mental training on sequential effect that we didn't test in our work

We suggest that the putative neural model that we implemented may serve as a marker of mental fatigue which considered as a very frequent symptom within many neurodegenerative diseases such multiple sclerosis (MS), chronic and fatigue syndrome (CFS). It would be interesting to examine this model within these clinical populations who suffer from the inability to sustain attention for a long period o f time

Chapter 4/ Study C: Cortisol activity and relation to mental and physical effort

Summary

Here in this study we aim to investigate within heathy population cortisol activity changes according to mental and physical effort. Thirteen participants were scanned during a reaction time task (physical group "grP") and a motor imagery task (mental group "grM") lasting 15 minutes each one. We collected Saliva samples before and after the task accomplishment (either physical or imagery task). In the brain we focus our hypothesis on brainstem and hypothalamus as being central components of the stress system: the hypothalamic-pituitary-adrenal (HPA) axis and having a major role in cortisol regulation. Cortisol levels were found to be higher and had greater reduction in levels during mental versus physical task. Activity of the brainstem and hypothalamus was more significant and spread within mental group compared to physical group. At low cortisol levels, individual analysis showed, less brainstem and hypothalamus activity within mental group participant (P2). Wider spread recruitment of these brain regions was observed at high cortisol levels (p9). This study shows that hypothalamus and brainstem may play a major role in the regulation of cortisol secretion in response to cognitively demanding situation. We suggest that cortisol would constitute a physiological marker of mental effort.

I) Introduction

Fatigue is a somatic state experienced by up to 40% of the general population (Ricci, Chee, Lorandeau, & Berger, 2007; Van'T Leven, Zielhuis, Van Der Meer, Verbeek, & Bleijenberg, 2010; Simon Wessely, Chalder, Hirsch, Wallace, & Wright, 1997) and described as having an important impact on daily life abilities (Hewlett et al., 2005; Lerdal, Gulowsen Celius, Krupp, & Dahl, 2007). It is known as being an extremely frequent symptom in many clinical populations (Barnes and Bruera, 2002; Sullivan and Dworkin, 2003; Krupp et al., 2010). Cortisol has been linked to fatigue in a number of studies of clinical and case—control studies on post-traumatic stress disorder, chronic fatigue syndrome (CFS) and fibromyalgia, suggesting reduced adrenal corticosteroid cortisol levels in all these syndromes (A. D. L. Roberts et al., 2004)I n which fatigue is a common symptom (Fries et al., 2005; Nater et al., 2008). Also, some other studies have related lower levels of cortisol in the morning to lower vitality levels (Adam, Hawkley, Kudielka, & Cacioppo, 2006). This low cortisol levels may accentuate fatigue development or stimulate its progression later in the same day (ter Wolbeek, van Doornen, Coffeng, Kavelaars, & Heijnen, 2007)

There are several factors which could affect cortisol regulatory networks in the CNS. Two types of stressor have been identified; reactive and anticipatory stressors, which stimulate the HPA axis through activation changes in different brain regions involved in cortisol regulation (Herman et al., 2003). Reactive stressors are defined as real sensory stimuli, such as bodily injury, pain, or an immune challenge. However anticipatory stressors are manifested in such unfamiliar situations or social challenges (Dedovic et al., 2009). Reactive stressors are known to implicate brainstem and the hypothalamus (Herman et al., 2003) whereas, anticipatory stressors tend to engage limbic system regions particularly the HC, the amygdala AG and medial PFC areas (Herman et al., 2003). A physical stressor could be like facing a wild animal, or the anticipation of bodily injury, however a social evaluative threat could be considered as a psychological stressor (Dickerson & Kemeny, 2004).

In the brain the regulation of cortisol secretion depends of the nature of the stressor factors (physical or psychological). Diverse neuroimaging and animal studies on brain activity changes in response to stress suggest contribution of limbic system regions such as the HC, the AG, and the PFC and the brainstem in physical stress (Dedovic et al., 2009). These structures stimulate and exercise a control on the HPA axis to modulate cortisol activity according to each situation.

In previous studies, Dedovic and colleagues (Dedovic et al., 2009) found significant interaction between cortisol release and fatigue in the right hippocampus with significantly decreased activation over time. Also decreased activity in orbitofrontal PFC has been demonstrated with increased cortisol secretion in response to a psychological stress task (J. C. Pruessner et al., 2005; J. Wang et al., 2005). Similarly, increased activity in medial PFC regions correlates with decreased cortisol secretion (Kern et al., 2008), because of projections emanating from the ventrolateral PFC towards the HC. This mechanism could allow ventrolateral PFC to decrease activity in orbital and medial PFC areas related to stress processing since this inappropriate control level could be associated with sustained cortisol secretion.

In addition, cortisol has been found to have a link with yawning known to be excessive in some neurological diseases (Thompson, 2010). It has been demonstrated that cortisol rises with excessive yawning with high rises in brain temperature (Thompson & Simonsen, 2015). (Lana-Peixoto et al., 2014) have also noted excessive yawning within patients who had neuromyelitis optica spectrum disorder (NMOSD). From MRI brain scans, their patients showed lesions in the brainstem and hypothalamus. Similarly adrenal insufficiency and Parkinson's disease is associated with excessive yawning. It is probable that the critical threshold level of cortisol is reached due to fatigue to elicit the yawning response and that this latter is due to an irregularity in the level of hormones within the HPA-axis. The British neurologist, Sir Francis Walshe, reported that patients with brainstem lesions had the capacity to raise their paralyzed arm when yawning. This has since been evidenced by a number of other researchers (Kang & Dhand, 2015; Walusinski, Neau, & Bogousslavsky, 2010). It is probable that there is a critical threshold for the level of cortisol before yawning occurs and is dependent upon fatigue, level of perception, and sleep deprivation.

Here in this study by using a protocol combining a mental task "motor imagery" known to mobilize a strong cognitive load, and a motor / physical task, we try to investigate within healthy population cortisol activity and its relation to mental and physical effort. We focus our hypothesis on brainstem and hypothalamus as key regions and we predict that the recruitment of brainstem and hypothalamus regions, important in cortisol activity, would be affected differently.

So we hypothesize that cortisol level would be higher during the motor imagery task which would require higher and wider hypothalamus and brainstem spread region activity comparing to physical task since mental task would be perceived as more cognitively demanding and more stressful than the physical task.

II) Method

1) Participants

13 healthy participants (6 males, 7 females) aged between 21-35 years (SD = 4.50) with no known history of neurological, psychiatric or sensorimotor disorders gave their prior, written, informed consent to participation in the study. All participants were recruited among STAPS (Sciences et Techniques des Activitiés Physiques et Sportives) students from Paris Ouest University and were granted 50 euros to optimize motivation and concentration. Participants were assessed using the Edinburgh inventory [37] for right-handedness, and with consent, were recruited at Pontoise Hospital Centre and University of Versailles- Saint-Quentin, France.

2) fMRI paradigm

Laying in the scanner, participants were asked to focus attention on a fixation cross in the Centre of the screen (5 degrees visual field) and squeeze the handle with the left hand as quickly as possible with different levels of force (low, medium, high) when a white square appeared. Force levels were pseudo-randomized to prevent possible order-effect and so that fatigue set in gradually and fairly throughout the paradigm. Half of participants performed the physical task first (grP; n=6). The rest of participants performed the imagery task first (grM; n=7). They were asked to attend to the imperative stimulus (white square) (for 15 mins) but "imagining" squeezing the handle (without actually squeezing it) trying to respect the level of force. Participant was instructed not to move his/her head for the duration of the acquisition and should always be focused. Before entering the fMRI, the participant was familiarized with the protocol.

3) Cortisol analysis

Saliva samples were collected before (sample 1 "S1") and again at the end of the run (either mental or physical) (Sample 2 "S2") from each participant. Each sample was analyzed and

destroyed after analysis. Data was held securely and coded to ensure anonymity of participants. Cortisol levels are easily and reliably measured in saliva and it is far less invasive than intravenous collection methods. Presence of cortisol in saliva is highly correlated with blood assay and cheaper to analyze in the specialized laboratory.

Data collected from analyzing the saliva cortisol samples was performed using SPSS software. Normative data for saliva cortisol lies within the ranges: (i) Morning collection: 3.7-9.5 nanograms per millilitre of saliva; (ii) Noon collection: 1.2-3.0 nanograms per millilitre; and (iii) Evening collection: 0.6-1.9 nanograms per millilitre.

4) SPM analysis

Image processing was performed using Statistical Parametric Mapping (SPM12) software (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). EPI volumes were corrected to adjust for within-volume time differences and realigned with the last volume to correct for head movements. Functional scans were spatially normalized against the standard, stereotactic space of the MNI. Spatial smoothing was performed with 8mm t Gaussian kernel. Haemodynamic responses were modelled as a box-car function convolved with a synthetic haemodynamic response function. Imaging analysis were conducted using only two putative regions of interest: midbrain and hypothalamus.

a) Group and individual analyses

Fixed-effect model was created for each individual subject in order to perform the based-conditions random-effect analysis (one sample *t* test for group analysis). To assess fatigue effects induced by both tasks, two contrasts were defined to compare the last bloc with the first bloc of the whole task. "Motor_late Vs Motor_early" and "Mental_late Vs Mental_early". In each single-subject analysis, a significance level of p = .05 was used to detect activated voxels for this contrast and corresponding mask.

b) ROI analysis

From a priori hypotheses reported in the literature, analysis of regions of interest (ROI) was conducted to compare activation changes between the beginning and end of the task. Two masks were applied using WFU PickAtlas software (http://fmri.wfubmc.edu/software/pickatlas) for the hypothalamus and the midbrain. WFU PickAtlas toolbox automatically generated segmented atlas ROI templates in Montreal Neurological Institute (MNI) space [39].

III) Results

1) Saliva samples

Mean age of participants was 26.4 years (SD=4.70). In saliva cortisol sample 1 (S1), the means for participants in the mental group was 7.0 (SD=7.21), and for the physical group was 2.6 (SD=.74). In sample 2, the means were 5.6 (SD=5.56) for mental group, and 2.5 (SD=.83) for physical group. Hence, those in the mental condition had higher levels of resting and post-experiment saliva cortisol levels than those in the physical condition (Table 7).

Paired samples correlations showed for all participants, significant correlations between saliva cortisol sample S1 and sample S2 (P=.0001) (Table 8). When comparing means no significant difference was found (P=.247) (Table 9). For mental group, Paired samples correlations showed significant correlations between samples (S1 vs S2) (P=.002) (Table 10). No significant correlation was seen in the physical group (P=.469) (Table 11). Using paired samples test, means testing did not reveal differences between samples for both groups condition (Tables 12 and 13).

P	***Sexe***	***AGE***	***S1***	***S2***	***PERIOD***	***MentPhys***
P1	M	34	2.3	2.3	Morning	P
P2	F	30	2.6	2.3	Noon	M
P3	M	35	4.5	4	Morning	M
P4	M	27	1.9	1.9	Noon	P
P5	F	23	3.6	6.9	Noon	M
P6	F	21	2.8	3.1	Noon	P
P7	F	21	5.9	3.6	Morning	M
P8	F	29	4	1.6	Noon	P
P9	M	23	22.7	17.7	Morning	M
P10	F	27	2.2	3.8	Morning	P
P11	M	25	1.8	2	Noon	M
P12	F	27	2.5	2.1	Evening	P
P13	M	21	7.6	3	Morning	M
P13	M	21	7.6	3	Morning	M

Table 7*: Cortisol level for all participants. P: Participants; M: male, F: female; S1, S2 = cortisol saliva sample; MentPhys: M=Mental, P= Physical*

Paired Samples correlation				
		N	Correlation	Sig.
Pair1	Sample1 & Sample 2	13	0.925	.000

***Table 8**: All participants – correlation of S1 with S2.*

Paired samples test									
		Paired differences					t	df	Sig (2-tailes)
		Mean	Std.dev	Std.err mean	95% confidence interval of the difference				
					Lower	Upper			
Pair 1	S1&S2	0.77692	2.29933	0.63772	-0.61255	2.16639	1.218	12	0.247

***Table 9**: All participants – means of S1 compared with S2*

Paired Samples correlations				
		N	Correlation	Sig.
Pair 1	Sample1& Sample2	7	0.929	0.002

***Table 10**: Mental condition – correlation of S1 with S2*

Paired Samples correlations				
		N	Correlation	Sig.
Pair 1	Sample1& Sample2	6	-.371	0.469

***Table 11**: Physical condition - correlation of S1 compared with S2.*

Paired samples test									
		Paired differences					t	df	Sig (2-tailes)
		Mean	Std.dev	Std.err mean	95% confidence interval of the difference				
					Lower	Upper			
Pair 1	S1&S2	1.314	2.904	1.097	-1.372	4.000	1.197	6	.276

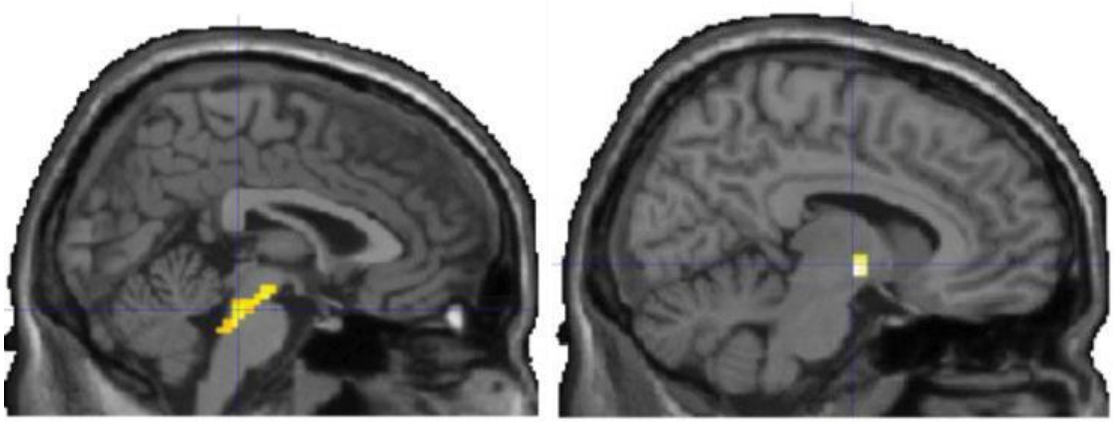
Table 12: *Mental condition – means of S1 compared with S2.*

Paired samples test									
		Paired differences					t	df	Sig (2-tailes)
		Mean	Std.dev	Std.err mean	95% confidence interval of the difference				
					Lower	Upper			
Pair 1	S1&S2	0.15	1.29885	0.53025	-1.21305	1.51305	0.283	5	0.789

Table 13: *Physical condition - means of S1 compared with S2.*

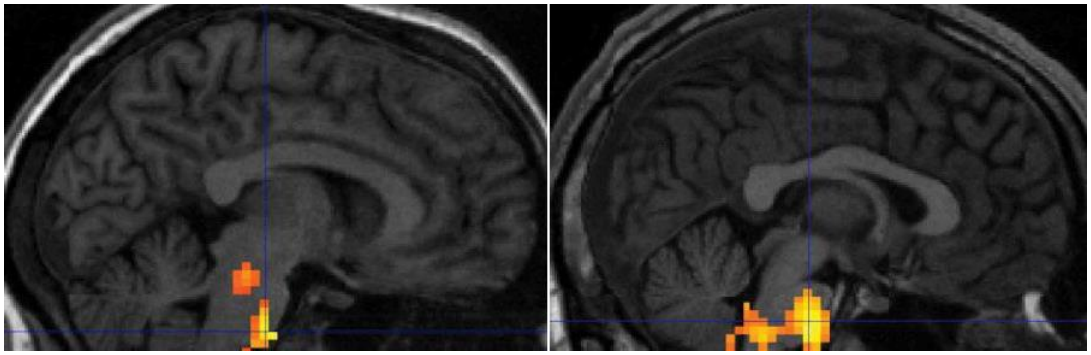
IV) Imaging results

Comparison between the two groups (grM and grP) revealed increased activity in our regions of interest (brainstem and hypothalamus) (figure22). Individual analyzes showed that for participants with lower cortisol level (P2 in grM and P4 in grP) brainstem and hypothalamus activity was less significant and less spread within P2 compared to P4 (figure 23/24). However, when comparing participants with the highest level of cortisol (P9 in grM and P10 in grP), more spread activity was observed only in the brainstem in P9 compared to P10.



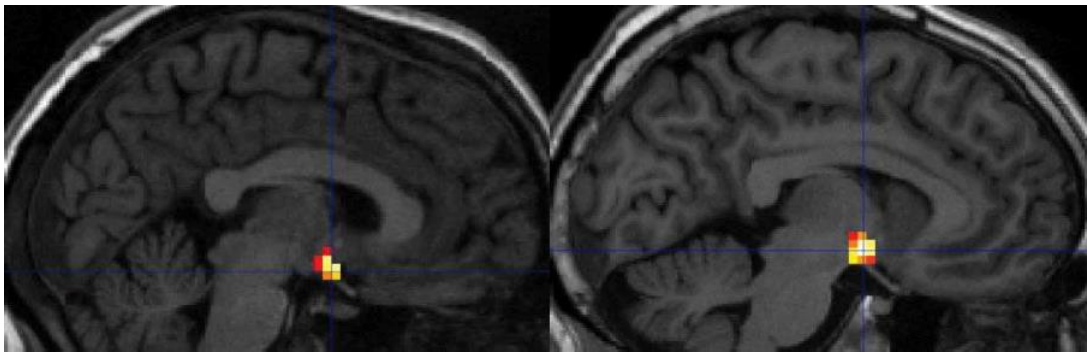
Brainstem Hypothalamus

Figure 22: *Brain scans comparing brainstem and hypothalamus activity as an average across "Mental versus Physical" participants.*



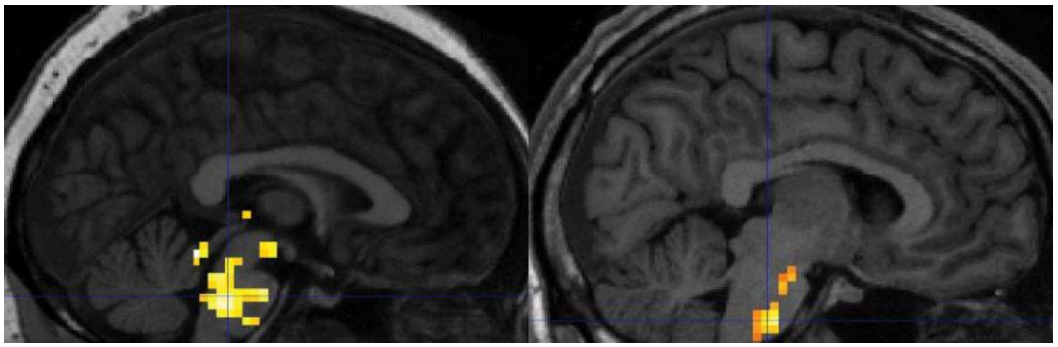
P2 Mental P4 physical

Figure 23: *Brain scans comparing brainstem activity in mental and physical tasks for lowest level of cortisol.*



P2 Mental P4 Mental

Figure 24*: Brain scans comparing hypothalamus activity in mental and physical tasks for lowest level of cortisol.*



P9 Mental P10 physical

Figure 25: *Brain scans comparing brainstem activity in mental and physical tasks for highest levels of cortisol.*

V) Discussion

The present study provides preliminary results about the relation between cortisol secretion and mental effort within healthy population. When comparing globally the physical with the mental group, the mental group showed higher and more changes in cortisol levels compared to the physical group. This result demonstrates that the motor imagery task, perceived as stressful, was more demanding in term of cortisol secretion. In the brain, comparison between both groups (Mental group>physical group), showed increased activity in the brainstem and hypothalamus regions.

Individual analysis showed, for the physical group, increased activity in the brainstem and hypothalamus within the participants with the lowest level of cortisol (P4). This activity was less significant and less spread in the brainstem within the participants with the highest level of cortisol (P10). In the mental group, results showed more significant and spread brainstem activity within the participant with the highest cortisol concentration (P9) compared to the participant with the lowest cortisol level (P2).

These findings suggest that brainstem and hypothalamus may have a crucial role in cortisol regulation under cognitively demanding task. In fact the brainstem constitutes the center of the arousal system. It provides bottom-up noradrenergic stimulations necessary for the maintenance of the arousal. These stimulations pass through the thalamic gates to cortical

structures (anterior cingulate cortex, prefrontal and parietal cortex) (Jones 2003). The bottom-up control is coming mainly from the ponto-mesencephalic part of the brainstem (Clemens et al., 2011, 2013). In addition, the brainstem, in particular the noradrenergic neurons of the locus caeruleus, represent a main structure of the stress system (Papadimitriou and Priftis 2009) in addition to the CRH (corticotropin-releasing hormone) and AVP (arginine vasopressin) neurons of the hypothalamic paraventricular nuclei (PVN) which constitute the starting point of the cortisol regulatory circuit. some CRH fibers in the PVN project to the brainstem (Majzoub, 2006). On the other hand, CRH neurons of the PVN receive projections from brainstem noradrenergic pathways (Papadimitriou & Priftis, 2009). So anatomically brainstem is strongly related to the stress and arousal systems

Thus, during a continuous cognitive task an individual's adaptive response to excessive stress induced by the task involves interactions between hormones of the stress system and the central nervous system (CNS) to protect the organism against stressful situation on one hand (Selye, 1936) and an increase in arousal level to accomplish the task on the other hands. The brainstem activity increases and more noradrenergic signals are sent to cortical structures to provide an optimal level of arousal needed to complete the task. This increased activation of the brainstem will stimulate simultaneously the hypothalamus more particularly the hypothalamic paraventricular nuclei to trigger cortisol secretion circuit

When the effort is prolonged over time, the activity of the brainstem decreases leading to a decrease in noradrenergic stimulations sent to the cortical structures (decrease of the arousal) and to the hypothalamus (decrease of the cortisol concentration). Therefore, cortisol seems to be related to arousal activity. Moreover, (Kahneman 1973) considers that mental effort, in its physiological manifestations, is a particular case of arousal. Cortisol would therefore constitute a physiological marker of mental effort since it is directly related to the activity of arousal. Thus, the brainstem and the hypothalamus could be two key regions involved in the regulation of cortisol secretion in response to a cognitively demanding situation.

VI) Conclusions

The most consistent finding of this study is that increased activity in brainstem and hypothalamus was associated with increased cortisol during the mental task. However at lower cortisol levels brainstem and hypothalamus activity was found to be increased for physical more than mental task. These findings are encouraging because impairment in brainstem and hypothalamic regions, important to vital and healthy functioning, would be indicative of HPA-axis malfunctioning. It would be interesting for future research to deepen the investigation of the role that cortisol might play in the control of mental effort and extend our connectivity model by including these brain regions.

Perspectives Study C

This study shows that motor imagery task was more demanding in term of cortisol secretion compared to the physical task. This cortisol increase was associated with increased brainstem and hypothalamus brain regions activity. It would be of interest for future researches to investigate more deeply, within an effective connectivity model or graph theory, a wider network comprising regions involved in the regulation of cortisol and known to have an impact on the regulatory activity of the hypothalamic-pituitary-adrenal (HPA) axis.

Cortisol is a pure physiological component which changes with environmental changes and depends on physiological factors (circadian rhythm and the physiological clock), on sex, on individual characteristics (responders or not responders) and other psychological factors. To better understand cortisol activity and its fluctuations as a function of mental effort, it would be of interest to develop further studies that take into consideration all of these factors by implementing a particular protocol investigating genetic and environmental factors that could have an impact on the HPA axis and the neighboring systems. New developments in imaging techniques should facilitate this kind of challenges. Furthermore, studies on cortisol regulation as a response to physical stressors still needed within the field of scientific research to better understand the involvement of brainstem nuclei.

It is possible that cortisol levels fluctuate with atrophy and the demand for cortisol may alter according to structural changes in brain regions. Therefore, there is scope for investigating further the regional versus global changes in grey matter atrophy seen in multiple sclerosis (D'Souza et al., 1996; Lansley, Mataix-Cols, Grau, Radua, & Sastre-Garriga, 2013). Diffusion Tensor Imaging (DTI) and Voxel-Based Morphometry (VBM) are useful techniques for identifying atrophy in brain regions in neurological disease. Finally, taking together, these multidisciplinary approaches would help the researchers gaining an even greater understanding the functional neuroanatomy of cortisol regulation.

General conclusions

The work of this thesis focused on two major axis. the first one consists on understanding the temporal aspects of attention, its deployment and its limits as a function of time. The second axis focused on the identification of psychological, neural and physiological markers of mental effort for a better characterization of mental fatigue described in everyday life and particularly in clinical population such as multiple sclerosis and fatigue syndrome.

The findings of this thesis demonstrate that alertness with its two components (intrinsic and extrinsic) and the foreperiod (FP) parameter have served to understand the temporal processing of attention and mental effort effects. Using an alertness task with varied FP durations design preceded by an intensive session of motor imagery, has enabled us to build a first neural model (AI-ACC-DLPFC) that we assume responsible for temporal processing. We were able, to show, through the first study of this thesis work, that motor imagery has optimized the temporal preparation particularly for short FP scale for both alertness tasks. This performance improvement was associated with an increase in connectivity of AI-ACC and AI-DLPFC circuits during intrinsic alertness and DLPFC-ACC during extrinsic alertness. The originality of this work is that we were able, through our protocol, to modulate arousal on very short temporal scale (<1s). We have redefined the optimal threshold of arousal for both alertness tasks, in other terms we have reduced, by mental training, the duration in which arousal can reach its optimal peak according to each alertness task.

In the second study we showed that when mental load is handled for long time, sustained attention decreased during intrinsic alertness and leaded somehow to mental fatigue state manifesting in increased RTs. This RT increase was observed also during short FPs and associated with effective connectivity decrease of AI-ACC and AI-DLPFC circuits which were sensitive to mental fatigue. This finding is of big interest in indicating that mental fatigue has impacted both arousal and the temporal processing and that AI-ACC-DLPFC network could therefore constitute a neural marker of mental effort. This study finding confirms the fact that short FPs were more sensitive to arousal modulation (increase by mental training and decrease with sustained mental effort).

In the third and last study we tried to show that cortisol would be a physiological indicator of mental effort. We were able to demonstrate that arousal and cortisol are subject to same rules and principles and controlled by a common neural structure which is the brainstem. During a cognitive demanding task, the brainstem stimulate through noradrenergic afference both

arousal system (cortical regions involved in the control of arousal) and stress system (the hypothalamus to trigger cortisol secretion) since cognitive load generates at least in part a mental stress. So arousal and cortisol are directly related and function in parallel; they increase with increased cognitive demands and decrease as a result of mental fatigue.

Taking together, AI, ACC, DLPFC, hypothalamus and the brainstem would constitute a neural basis in understanding mental effort mechanisms. It would be advisable for further researches to integrate these regions in a single connectivity model in which the brainstem would be considered as the central component (hub region) of the neural model. It would also be interesting to couple brain activity with physiological measures (heart rate, respiration, pupil dilation, electro-dermal response) and to adjust the durations of FPs on a time scale as close as possible to the physiological measurements allowing better characterize the effects of arousal on mental effort and fatigue.

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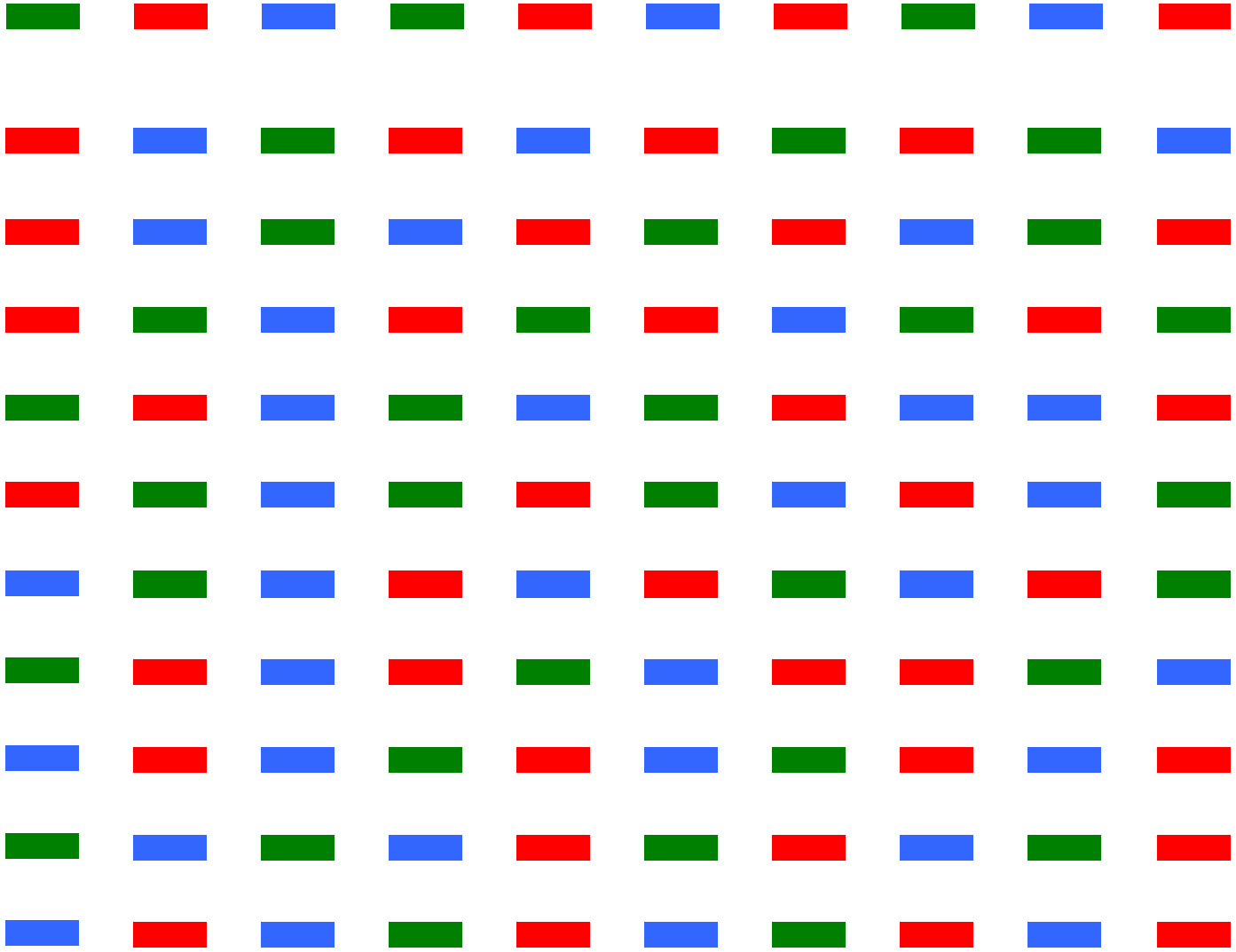
Appendix

Stroop test



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Appendix

Test d 2

Date : _____ N° : _____

Nom : _____ Prénom : _____

Profession : _____ Age : _____

Exemple : $\overset{''}{d}$ $\underset{''}{d}$ $\underset{'}{\overset{'}{d}}$

Essai :

$\overset{''}{d}$	$\overset{''}{p}$	$\underset{'}{\overset{'}{d}}$	$\underset{'}{d}$	$\overset{''}{d}$	$\underset{''}{d}$	$\overset{''}{p}$	$\underset{''}{\overset{'}{d}}$	$\underset{''}{d}$	$\underset{'}{\overset{'}{p}}$	$\underset{'}{d}$	$\overset{''}{d}$	$\underset{''}{d}$	$\underset{''}{\overset{'}{d}}$	$\underset{''}{\overset{'}{p}}$	$\overset{''}{p}$	$\underset{''}{d}$	$\underset{''}{\overset{''}{d}}$	$\overset{''}{d}$	$\underset{''}{p}$	$\underset{'}{d}$	$\underset{'}{\overset{'}{d}}$
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22

	RW	%	PR	SW
GZ		–		
F				–
GZ – F		–		
SB		–		–
Répartition des fautes				

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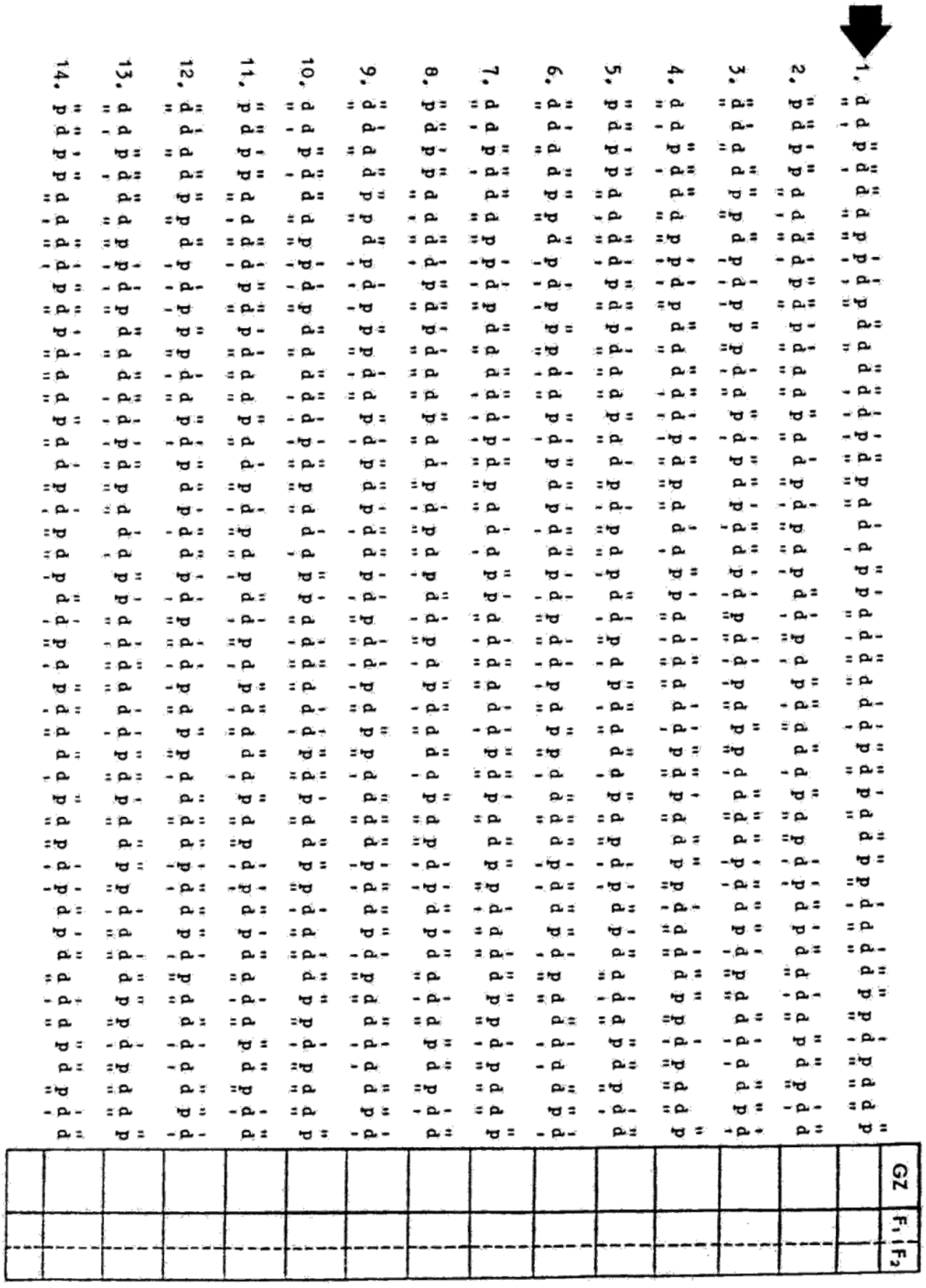
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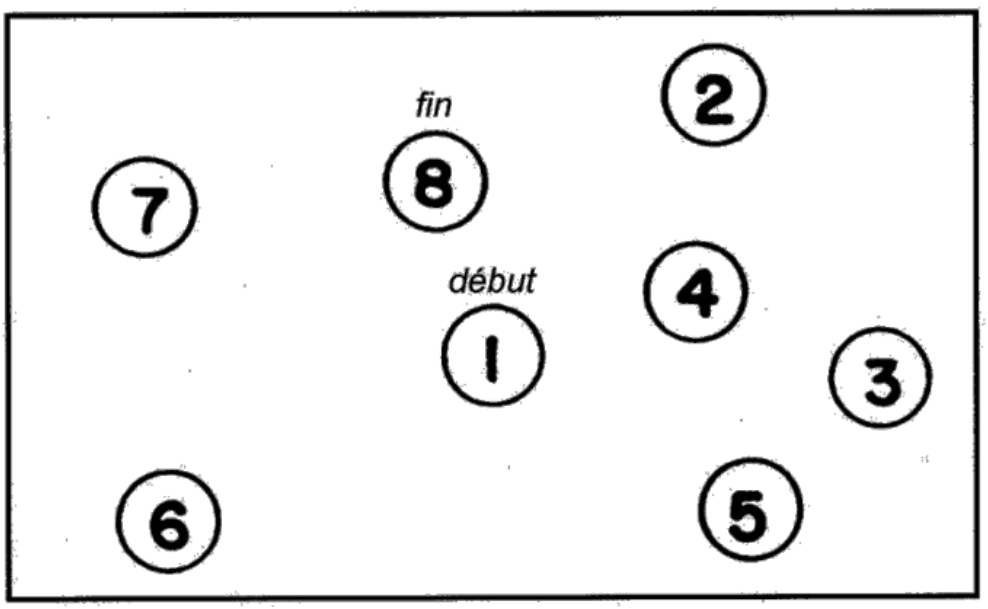
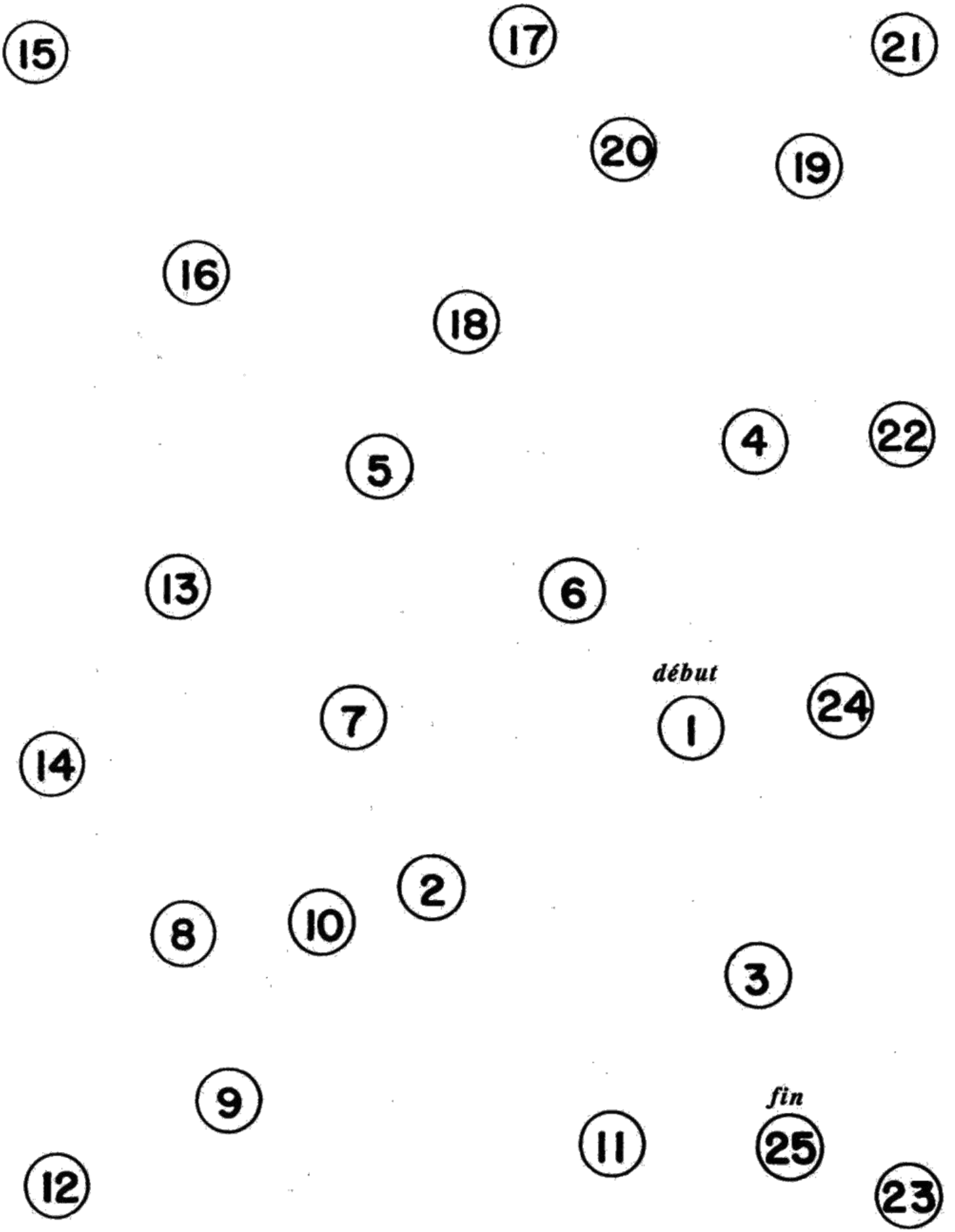
TRAIL-MAKING

Partie A

EXEMPLE

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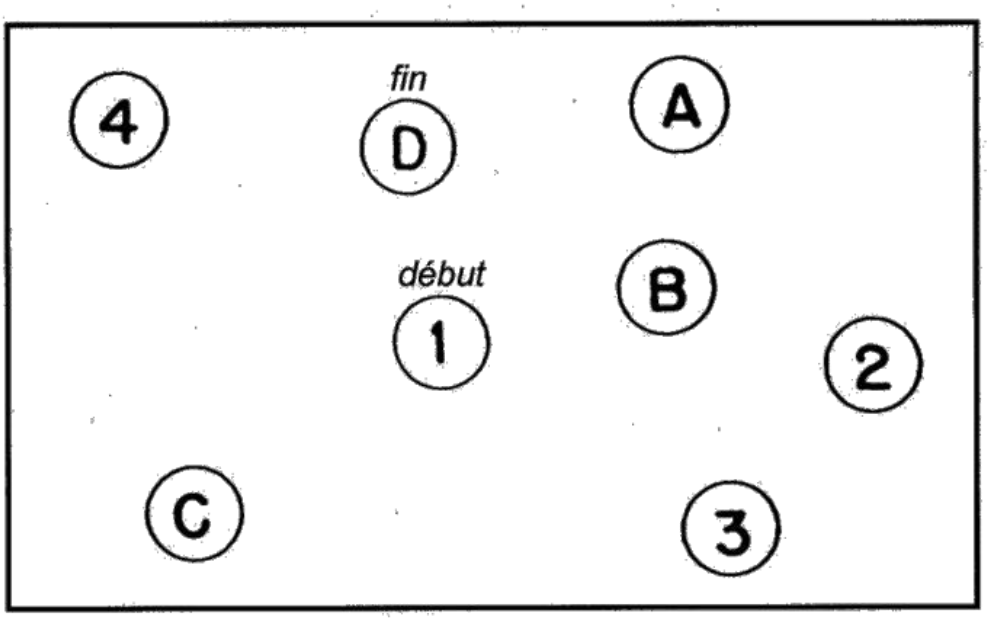
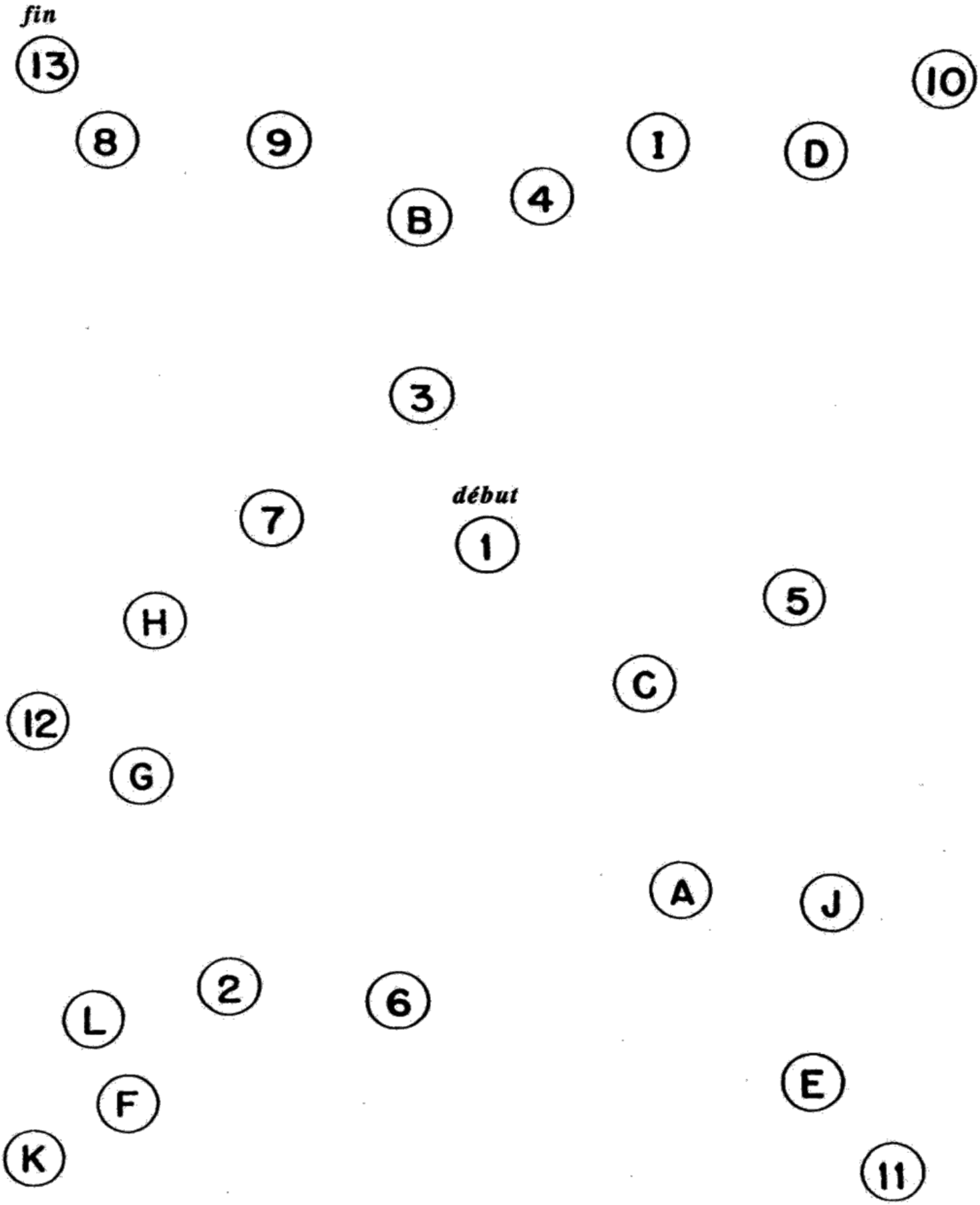
TRAIL-MAKING

Partie B

EXEMPLE

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BORG RATING OF PERCEIVED EXERTION (RPE) SCALE

Number rating	Verbal rating	Example
6		No effort at all. Sitting and doing nothing.
7	Very, very light	Your effort is just noticeable.
8		
9	Very light	Walking slowly at your own pace.
10		Light effort.
11	Fairly light	Still feels like you have enough energy to continue exercising.
12		
13	Somewhat hard	
14		Strong effort needed.
15	Hard	
16		Very strong effort needed.
17	Very hard	You can still go on but you really have to push yourself. It feels very heavy and you're very tired.
18		
19	Very, very hard	For most people, this is the most strenuous exercise they have ever done. Almost maximal effort.
20		Absolute maximal effort (highest possible). Exhaustion.