

University of Groningen

In the heat of the moment

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DOI:
[10.33612/diss.109887653](https://doi.org/10.33612/diss.109887653)

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

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

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Soto Padilla, A. (2020). *In the heat of the moment: How Drosophila melanogaster's response to temperature is modulated by sensory systems, social environment, development, and cognition*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.109887653>

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General Synthesis

Andrea Soto Padilla

Environmental factors, such as light, humidity and temperature, apply selective pressures that determine what types of organisms can thrive in different ecosystems. When environments change, as when mean temperatures increase, organisms are forced to adapt to the new conditions to survive. For example, the higher temperatures brought by the recent acceleration in climate change led species of birds, squirrels, and flowering plants to breed and bloom earlier in the year (Dietzl et al., 2007; Nussey et al., 2005; Réale et al., 2003), whilst species of mosquitos have began to remain active for longer before going dormant for the winter (Bradshaw and Holzapfel, 2001). Meanwhile, extreme weather events (temperatures above a given threshold for an area; in Coumou and Rahmstorf, 2012), caused by the shifting climate, have produced the death of desert bird species, coral reefs, and trees (Allen et al., 2010; Hughes et al., 2003; McKechnie and Wolf, 2010).

Temperature changes have a dramatic influence on organisms' survival because temperature directly affects the rate at which enzymatic reactions occur. Enzymes are the main catalyst of all biochemical reactions required for life; lower temperatures produce slower enzymatic activity, while higher temperature lead to faster enzymatic action (Santhosh, 2018). However, enzymes are incapable of working at all temperatures; below a minimum temperature enzymes will lack sufficient energy to produce a biochemical reaction, while beyond a maximum temperature, enzymes denaturalize and decouple from their substrates, preventing them from working (Huey and Kingsolver, 1989; Martinez del Rio and Karasov, 2010). This implies that organisms are restricted to spending their lives within temperature ranges at which their enzymes can function to ensure their survival (Martin and Huey, 2008). As temperature in the wild fluctuates through multiple time scales, from seasonal changes to daily thermal variations (Colinet et al., 2015), organisms have evolved two main mechanisms to maintain their body temperature within the permissive limits: endotherms, on the one hand, use physiological processes to actively regulate their body temperature; ectotherms, on the other hand, adapt to thermal variations using behavioural responses through which they seek areas that are in their temperature tolerance range (Abram et al., 2017).

Ectotherms are divided in large and small organisms. Large ectotherms, such as lizards and turtles, have a large body mass that delays the effects of heating and cooling and allows them to tolerate abrupt temperature changes without immediate metabolic consequence (Stevenson, 1985). Meanwhile, small ectotherms such as insects acquire the temperature of their environment almost instantly (Angilleta, 2006; Stevenson, 1985), which quickly translates into metabolic and behavioural changes. For example, temperature predicts ants' walking speed with such accuracy that ant locomotion can be used to determine how warm it is (Martinez del Rio and Karasov, 2010). The close relationship between temperature, biochemical reactions, and insect behaviour, permits using principles of enzyme kinetics to represent insect's thermal performance curves (Logan et al., 1976). This could create the impression that insect behaviour is no more than the reflection of the direct effect of temperature on the rate of their biochemical reactions. However, a closer inspection of the insect world has revealed examples that question this conclusion: triatomid bugs and migratory locusts change their temperature preference according to their nutritional status (Coggan et al., 2011), probably to increase the assimilation of certain nutrients at a more efficient thermal range (Clissold et al., 2013); some species of cockroaches prefer colder environments when environmental humidity is low (Deal, 1941; Gunn, 1933), indicating a combined effect of moisture and thermal information; and worker ants deprived of certain nutrients seek lower temperatures (Porter and Tschinkel, 1993), most likely to increase their longevity when resources are limited. These observations suggest that insects combine external and internal stimuli to control their behavioural response to temperature (Gallio et al., 2011), and that they are not simple victims of changes in enzymatic processes. Most likely, the final behavioural output is a combination of the direct effect of temperature over insect's biochemical reactions and their capacity to integrate this effect with other physiological inputs to coordinate their response.

The work presented here tested the capacity of *Drosophila melanogaster* to adapt to diverse temperature challenges. The fly has been a fundamental research tool for over a hundred years (Bellen et al., 2010), helping us elucidate the mechanisms behind heredity, development of the nervous system, behavioural regulation, and even social interactions (Bellen et al., 2010; Ramdya et al., 2017). Temperature studies have shown that flies possess a complex temperature sensing system, with central and peripheral receptors dedicated to particular temperature ranges or rates of temperature change (Frank et al., 2015; Gallio et al., 2011; Hamada et al., 2008; Luo et al., 2017; Ni et al., 2013; Tang et al., 2013). Flies also possess a neural substrate where temperature information appears to be integrated with other stimuli to regulate their behavioural response (Frank et al., 2017; Gallio et al., 2011). These findings mean that *Drosophila* can be used as model to understand how small ectotherms process temperature information to guide their behaviour, and to predict how climate change might affect the manner in which these organisms react. To test *Drosophila*'s response to thermal challenges, a device capable of fast and precise temperature changes controlled in time and space, where flies do not require frequent manipulation, was necessary. Development and implementation of such a device is presented in **Chapter 2** as a new temperature-controlled arena. In **Chapter 3**, flies were exposed to gradually increasing temperatures within this arena to explore the importance of their thermosensors in their locomotor response to temperature. Wild-type flies moved faster as temperature increased beyond their maximum threshold of comfortable temperatures ($>27^{\circ}\text{C}$), until a

maximum point of performance ($\sim 36^{\circ}\text{C}$) was reached, after which their speed decreased. Meanwhile, flies lacking central thermosensors did not increase speed at any temperature, while flies lacking a peripheral thermosensor increased speed but at a lower rate and maximum than wild-type flies. These data suggest that a functioning thermosensory system is required for flies to respond to changing temperatures, and confirms that insect's behavioural response to temperature is not based on a passive biochemical effects but on neural regulation. Nonetheless, future studies should consider exploring the biochemical effects of the thermosensory receptors related to temperature changes. Even though the final behavioural output of flies is linked to the cognitive handling of the temperature information, it is reasonable to expect that the function of the thermosensors directly relates to their biochemical response to changing temperatures. This would open the door to exploring how biochemical information is translated to cognitive processing and help understand the development and evolution of thermal adaptation.

Cognitive control over the temperature response allows *Drosophila* to regulate their thermal reaction according other relevant environmental factors. **Chapter 4** shows that male and female flies tested alone have similar temperature response curves. However, when surrounded by same-sex peers, individual male flies increased their speed at high temperature ($34\text{-}38^{\circ}\text{C}$), while female flies remain at a similar speed as females tested alone. Surprisingly, this sexual dimorphism depends on the perceived sex of the other group members: when male flies are modified to express female pheromones (identifying them as females to others), they stop increasing their speed in the presence of others, while females made to express male pheromones move faster when tested in a group. As the feminization and masculinization processes affects only the pheromones produced by the flies but not their internal state, it is safe to conclude that it is the perceived sex of the others that conditions this sexually dimorphic difference. One of the reasons behind this divergence between the sexes is the amount of interactions sought by male and female flies at high temperatures: females contact each other more often than males. Mutant females lacking mechanosensory receptors move faster at high temperatures than their wild-type counterparts, which suggests that touching each other reduces the intensity of the stress response of normal female flies. Mechanosensory mutant females also increase social interactions when exposed to high temperatures, which further supports that social contact is important for females to deal with stress, at least the one brought by increasing temperature. Interestingly, this resembles the response to stress of males and females of mammalian species: rodent, non-human primates, and human females have a strong inclination for seeking others when stressed (tend-and-befriend), while males often follow a fight-or-flight pattern (Genovesio et al., 2015; Taylor et al., 2000). Analyses of the functional and neurochemical patterns between males and females of mammalian species have shown that the larger concentrations of oxytocin and oxytocin receptors of females could produce a stronger natural drive to seek others, which could be exacerbated during stress as higher concentrations of oxytocin reduce the impact of the stress response (Taylor et al., 2000). *Drosophila* do not produce oxytocin; nonetheless, flies hold a sexually differentiated stress response system (Neckameyer and Nieto, 2015) that produces sexually specific changes in dopamine concentrations (Argue and Neckameyer, 2013). As the dopaminergic and oxytocin brain circuits are intimately integrated in mammals (Baskerville and Douglas, 2010; Love, 2014), it is possible that a common dopaminergic pathway could explain the sexually dimorphic response to stress of *Drosophila* and

mammalian grouped females and males. *Drosophila* possess a known dopaminergic system with multiple markers for specific dopaminergic clusters (Mao and Davis, 2009; Xie et al., 2018), which implies that the system presented here can be used to investigate the mechanisms linking the sexually dimorphic response to stress and its interaction with social context.

Temperature affects not only how *Drosophila* respond to their immediate environment, but also how fly species distribute around the world (Jezovit et al., 2017; Kellermann et al., 2012). Different fly species have adjusted their thermal tolerance to the temperature range of the environment in which they exist, which has led to species-specific reaction to the same thermal challenge, as illustrated in *Figure 3* of **Chapter 2**. Flies' adaptation to a particular temperature range suggest that some species might face an impossible challenge when exposed to the increasing temperatures worldwide due to climate change. In fact, climate change is considered one of the main contributors of insects' population loss in the past few decades and a predicted factor of future decline (Sánchez-Bayoa and Wyckhuys, 2019). Nevertheless, *Drosophila* might be able to quickly adapt to the changes around the world by transgenerational effects in which parents equip their offspring to better face future challenges. For example, flies from parents raised at 25°C or 29°C showed higher fitness than offspring from parents kept at 18°C (Gibert et al., 2001), while offspring from parents kept at either 18°C or 29°C survived more often when kept at the same temperature of their parents than when placed in the opposite environment (Mohan et al., 2018). These data suggest that *Drosophila* is able to use temperature information of their current environment as a cue to affect the development of their offspring and better prepare them for the environment they will face. At the same time, flies possess physiological mechanisms to respond to thermal fluctuations of daily life that do not require parental influence (Colinet et al., 2015). For example, flies exposed to brief periods of high temperature overproduced heat-shock proteins, which allows them to tolerate future periods of thermal stress (Roberts et al., 2003), while flies exposed to short moments of coldness have a metabolic transition from forming glycogen storages to increasing triglyceride stores, which augments their cold resistance (Marshall and Uller, 2007). These data suggest that individual phenotypic plasticity is sufficient to allow flies to adjust to new temperature environments, irrespective of the experience of their parents. As shown in the match and mismatch design of **Chapter 5**, in which mothers were exposed to 29°C (hot) or 18°C (cool) and their offspring developed and the same temperature or at the other temperature, the main contributor to a fly's response to thermal challenges is the environment in which that fly developed. Flies that grew in a hot environment recovered faster from heat-shock and had an overall faster movement, probably linked to a faster metabolism, than flies from a cool environment. Meanwhile, flies from a cool environment recovered faster from cold-shock than flies from a hot environment, demonstrating a greater cold resistance. However, offspring from 29°C mothers move faster in the climbing test and when exposed to gradually increasing temperatures, while offspring from 18°C mothers recovered faster after cold- or heat-shock, regardless of offspring environment. This suggests that maternal influence played a role in determining the fly's capacity to respond to temperature challenges. Maternal influence could have emerged from an anticipatory mechanism from the mothers after their sudden exposure to 29°C or 18°C; conversely, it could have arisen as a carry-over effect of physiological changes occurring in the mothers that allowed them to produce better or worse quality

eggs. Future studies should focus in segmenting these two possibilities by analyzing genetic changes in mothers and offspring and metabolic differences between flies from either environment. It would also be advisable to observe offspring at different development stages, as maternal effects could be stronger during early larvae stages (24-48 hours after egg-laying), where individuals may not yet have a formed thermosensory system and may still rely on accurate information from their parents. Another interesting angle would be to analyze fly species adapted to diverse climate niches, as cosmopolitan species, such as the ones used in **Chapter 5**, might depend more on environmental influence to determine their temperature tolerance while highly specialized lineages might have a stronger transgenerational component. Describing the details behind transgenerational and individual effects in diverse fly species could help predict how insects will adapt to climate change and how the current biodiversity might change in the coming decades.

The fast adaptation of *Drosophila melanogaster* to changing temperatures suggests that temperature changes could be used as particularly salient stimuli to explore other behaviours. In fact, flies response to temperature has been used to explore the genetic basis of memory and learning (Ofstad et al., 2011; Putz and Heisenberg, 2002; Wustmann and Heisenberg, 1997; Wustmann et al., 1996; Zars and Zars, 2006; Zars et al., 2000), which suggests that other cognitive skills could be explored based on thermal response. In **Chapter 6**, flies were exposed to long and short visual or auditory stimuli paired with temperature changes to condition them to move to a particular area based on the presented stimulus. The intention was to demonstrate that flies could differentiate between short and long durations and hence that they could be used as a model of short-range time perception, known as interval timing. Interval timing is a fundamental component of learning, decision-making, and numerous other cognitive functions (Buhusi and Meck, 2005; Matell and Meck, 2000), neural bases of which still remain unknown. *Drosophila* could have served as a model of the wiring diagram at the single neuronal level (Kohl and Jefferis, 2011) of interval timing had they demonstrated to possess this skill. However, although flies demonstrated an ability to follow the temperature gradients they were exposed to, they did not show interval timing. This does not imply that *Drosophila* absolutely lack interval timing capacity, as it could reflect that this paradigm was not ideal to demonstrate this process in the fly. Further attempts could consider using other conditioning stimuli, such as a food reward, or other experimental set-ups, such as observing flying bouts, to fully explore interval timing in *Drosophila* and take advantage of the fly to understand this cognitive process.

Final Remarks

Drosophila melanogaster is a fascinating research organism. Flies permit answering questions from the neuron-by-neuron level to the population perspective, allowing us to explore genetic, physiological, behavioural and evolutionary components of a multitude of processes. Not surprisingly, flies have been fundamental in the understanding of male and female interactions (Billeter et al., 2009; Gorter et al., 2016; Laturney and Billeter, 2014; Yamamoto and Koganezawa, 2013), egg laying (Duménil et al., 2016), circadian rhythms (Yao and Shafer, 2014), sleep cycles (Donlea et al., 2014), learning and memory (Galili et al., 2011), temperature processing (Barbagallo and Garrity, 2015), and even social behaviour (Ramdya et al., 2015; Schneider et al., 2012). Temperature is a particularly relevant component of a fly's life as it affects all aspects of *Drosophila's* existence, from their development (Kjærsgaard et al., 2012) and distribution (Jezovit et al., 2017), to their survival (**Chapter 5**) and social communication (**Chapter 4**). Many of these aspects, such as the response to gradually increasing temperature (**Chapter 3**) or to sudden temperature changes (**Chapter 3 and Chapter 6**), can be explored in the new temperature-controlled arena here developed (**Chapter 2**). However, some aspects still require new inventions and innovative approaches to be examined. For example, flying might allow flies to tolerate warmer environments by reducing their exposure to a hot surface and instead exposing them to wind, which increases heat loss. It would be interesting to explore how diverse interventions, such as developmental temperature or maternal environment, affect the rate at which flies fly and land, and what does a change in this rate imply for mating, egg deposition, and overall survival. One can imagine that if flies spend more time flying due to an increase in surface temperatures, their energy expenditure might increase and their opportunities to mate and lay eggs might reduce, leading to shorter lifespans and less successful reproductive attempts, which could translate into the extinction of a species. On the other extreme, flies in colder areas suffering from longer and more intense cold weather could develop new strategies to cope with this challenge, such as grouping more often and for longer periods to keep warm. This could lead to the development of new communications strategies, such as shorter-range pheromones substituting longer-range cues, and to new behaviors between males and females to control the rate of courtship and mating while grouped. It would be fascinating to develop a method in which the mechanisms behind this adaptation could be studied and unraveled.

The work presented here could also be further complemented by an exploration of the genetic and metabolic components of *Drosophila's* thermal response. Fly larvae that develop in cold or hot environments (13°C - 29°C) have differential gene expression (Chen et al., 2015), which suggests that genetic plasticity plays a fundamental role in conferring flies cold and hot resistance. It is worth exploring if adult flies are capable of the same genetic plasticity, and if these modifications could be inherited by the next generation, which could accelerate offspring adaptation to the impending climate change. It would also be interesting to investigate whether genetic changes in larvae correlate to changes in adulthood and whether these changes could restrict further adaptability later in life. Differences between species in these aspects could explain why some *Drosophila* inhabit multiple climates while others are restricted to specific temperature ranges. Knowing that some species might not be able to cope with the impending changes of climate change

could help predict how ecosystems might vary around the world and what consequences this might imply for human development and survival.

This thesis has covered diverse aspects of *Drosophila's* response to temperature. It has shown that flies must perceive temperature to properly react to it, that temperature affects how flies interact with each other, that the environment of mothers and offspring affects how flies respond to thermal challenges, and that flies can use temperature information to predict where they should move. It has also presented a new temperature-controlled arena that could be exploited to explore similar temperature-related aspects of other insects, or even of larger species if the technical components are properly adapted. Overall, this thesis demonstrates that temperature matters, and that understanding how the fly deals with it is fundamental for a deeper comprehension of this vital environmental factor, but also of principles that might affect other species, such as the impact of climate change, parental effects, and how brains integrate sensory information.

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